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(71) Applicant *(for all designated States except US)*: CENTOCOR, INC. [US/US]; 200 Great Valley Parkway, Malvern, PA 19355-1307 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HEAVNER, George, A. [US/US]; 6 Oak Glen Drive, Malvern, PA 19355 (US). KRUSZYNSKI, Marian [PL/US]; Apartment E-20, 1100 West Chester Pike, West Chester, PA 19382 (US). MERVIC, Miljenko [SI/US]; Apartment 201B, Valley Forge Apartments, King of Prussia, PA 19406 (US). WEBER, Robert, Walter [US/US]; 250 Milford Road, Downingtown, PA 19335 (US).

(74) Agents: ELDERKIN, Dianne, B. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).

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(54) Title: TUMOR NECROSIS FACTOR INHIBITORS

(57) Abstract

Peptides that consist of 4 to 25 amino acids and that inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor activity are disclosed. The methods comprise contacting tumor necrosis factor alpha with a peptide that comprises an amino acid sequence that consists of 4 to 25 amino acids and that inhibits tumor necrosis factor-alpha activity are disclosed. Methods of treating animals suspected of suffering from a disease or disorder mediated by tumor necrosis factor-alpha activity are disclosed. The methods comprise the step of administering to the individual a therapeutically effective amount of a peptide that comprises an amino acid sequence that consists of 4 to 25 amino acids and that inhibits tumor necrosis factor-alpha activity.

to TNFα with high affinity and can prevent TNFα from binding to its receptors. There is a need for compounds which can neutralize TNFα activity *in vivo*.

SUMMARY OF THE INVENTION

The invention relates to peptides that comprise an amino acid sequence that consist of 4 to 25 amino acids and that inhibit tumor necrosis factor-alpha activity. The peptides comprise at least a four amino acid residue fragment of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76. According to some embodiments of the invention, the peptides comprise at least a four amino acid residue fragment of:SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

The invention relates to peptides that have an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

The invention relates to methods of inhibiting tumor necrosis factor activity. The methods comprise contacting tumor necrosis factor alpha with a peptide that comprises an amino acid sequence which consists of 4 to 25 amino acids and that inhibits tumor necrosis factor-alpha activity. The peptide comprises at least a four amino acid residue fragment of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54,

SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76. According to the some embodiments, the peptide comprises at least a four amino acid residue fragment of:SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

The invention relates to methods of inhibiting tumor necrosis factor activity. The methods comprise contacting tumor necrosis factor alpha with a peptide that has an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

The invention relates to methods of treating animals suspected of suffering from a disease or disorder mediated by tumor necrosis factor-alpha activity. The methods comprise the step of administering to the individual a therapeutically effective amount of a peptide that comprises an amino acid sequence that consists of 4 to 25 amino acids and that inhibits tumor necrosis factor-alpha activity. The peptide comprises at least a four amino acid residue fragment of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76. According to the some embodiments, the peptide comprises at least a four amino acid residue fragment of:SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

The invention relates to methods of treating animals suspected of suffering from a disease or disorder mediated by

tumor necrosis factor-alpha activity. The methods comprise the step of administering to the individual a therapeutically effective amount of a peptide that has an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 (CCOR185) is a graph which shows data generated from experiments using peptides which are embodiments of the invention. The experiments were performed to evaluate dose dependent inhibition of TNFα by the peptides tested.

Figure 2 (CCOR140) is a graph which shows data generated from experiments using peptides which are embodiments of the invention. The experiments were performed to evaluate dose dependent inhibition of TNFα by the peptides tested.

Figure 3 (CCOR186) is a graph which shows data generated from experiments using peptides which are embodiments of the invention. The experiments were performed to evaluate dose dependent inhibition of TNFα by the peptides tested.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, compounds are provided which prevent TNFα from binding to p55 and p75 receptors. By inhibiting such TNFα/TNF receptor binding, the compounds of the invention inhibit the biological activity of TNFα. By blocking TNFα from binding to its receptors, the compounds of the invention prevent TNFα from producing the biological effect associated with the TNFα-TNF receptor binding.

The peptides of the present invention may be selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

In some embodiments, the peptides of the invention are peptides consisting of 4 to 25 amino acids. In some embodiments, the peptides consist of 20 amino acids or less. In some embodiments, the peptides consist of at least 8 amino acids. In some embodiments, the peptides consist of 8-20 amino acids. In some embodiments, the peptides consist of 10-15 amino acids.

According to some embodiments of the present invention, peptides comprise of amino acid sequences selected from the group consisting of: fragments of SEQ ID NO:21 that have at

least four amino acid residues, fragments of SEQ ID NO:22 that have at least four amino acid residues, fragments of SEQ ID NO:23 that have at least four amino acid residues, fragments of SEQ ID NO:42 that have at least four amino acid residues, fragments of SEQ ID NO:43 that have at least four amino acid residues, fragments of SEQ ID NO:44 that have at least four amino acid residues, fragments of SEQ ID NO:45 that have at least four amino acid residues, fragments of SEQ ID NO:46 that have at least four amino acid residues, fragments of SEQ ID NO:47 that have at least four amino acid residues, fragments of SEQ ID NO:48 that have at least four amino acid residues, and fragments of SEQ ID NO:49 that have at least four amino acid residues, fragments of SEQ ID NO:50 that have at least four amino acid residues, fragments of SEQ ID NO:51 that have at least four amino acid residues, fragments of SEQ ID NO:52 that have at least four amino acid residues, fragments of SEQ ID NO:53 that have at least four amino acid residues, fragments of SEQ ID NO:54 that have at least four amino acid residues, fragments of SEQ ID NO:55 that have at least four amino acid residues, fragments of SEQ ID NO:56 that have at least four amino acid residues, fragments of SEQ ID NO:57 that have at least four amino acid residues, fragments of SEQ ID NO:58 that have at least four amino acid residues, and fragments of SEQ ID NO:59 that have at least four amino acid residues, fragments of SEQ ID NO:60 that have at least four amino acid residues, fragments of SEQ ID NO:61 that have at least four amino acid residues, fragments of SEQ ID NO:62 that have at least four amino acid residues, fragments of SEQ ID NO:63 that have at least four amino acid residues, fragments of SEQ ID NO:64 that have at least four amino acid residues, fragments of SEQ ID NO:65 that have at least four amino acid residues, fragments of SEQ ID NO:66 that have at least four amino acid residues, fragments of SEQ ID NO:67 that have at least four amino acid residues, fragments of SEQ ID NO:68 that have at least four amino acid residues, and fragments of SEQ ID NO:69 that have at least four amino acid residues, fragments of SEQ ID NO:70 that have at least four amino acid residues, fragments of SEQ ID

NO:71 that have at least four amino acid residues, fragments of SEQ ID NO:73 that have at least four amino acid residues, fragments of SEQ ID NO:74 that have at least four amino acid residues, fragments of SEQ ID NO:75 that have at least four amino acid residues, and fragments of SEQ ID NO:76 that have at least four amino acid residues. In such embodiments, the peptides may further comprise additional amino acid residues.

According to some embodiments of the present invention, peptides consist of amino acid sequences selected from the group consisting of: fragments of SEQ ID NO:21 that have at least four amino acid residues, fragments of SEQ ID NO:22 that have at least four amino acid residues, fragments of SEQ ID NO:23 that have at least four amino acid residues, fragments of SEQ ID NO:42 that have at least four amino acid residues, fragments of SEQ ID NO:43 that have at least four amino acid residues, fragments of SEQ ID NO:44 that have at least four amino acid residues, fragments of SEQ ID NO:45 that have at least four amino acid residues, fragments of SEQ ID NO:46 that have at least four amino acid residues, fragments of SEQ ID NO:47 that have at least four amino acid residues, fragments of SEQ ID NO:48 that have at least four amino acid residues, and fragments of SEQ ID NO:49 that have at least four amino acid residues, fragments of SEQ ID NO:50 that have at least four amino acid residues, fragments of SEQ ID NO:51 that have at least four amino acid residues, fragments of SEQ ID NO:52 that have at least four amino acid residues, fragments of SEQ ID NO:53 that have at least four amino acid residues, fragments of SEQ ID NO:54 that have at least four amino acid residues, fragments of SEQ ID NO:55 that have at least four amino acid residues, fragments of SEQ ID NO:56 that have at least four amino acid residues, fragments of SEQ ID NO:57 that have at least four amino acid residues, fragments of SEQ ID NO:58 that have at least four amino acid residues, and fragments of SEQ ID NO:59 that have at least four amino acid residues, fragments of SEQ ID NO:60 that have at least four amino acid residues, fragments of SEQ ID NO:61 that have at least four amino acid residues, fragments of SEQ ID NO:62 that have at least four

amino acid residues, fragments of SEQ ID NO:63 that have at least four amino acid residues, fragments of SEQ ID NO:64 that have at least four amino acid residues, fragments of SEQ ID NO:65 that have at least four amino acid residues, fragments of SEQ ID NO:66 that have at least four amino acid residues, fragments of SEQ ID NO:67 that have at least four amino acid residues, fragments of SEQ ID NO:68 that have at least four amino acid residues, and fragments of SEQ ID NO:69 that have at least four amino acid residues, fragments of SEQ ID NO:70 that have at least four amino acid residues, fragments of SEQ ID NO:71 that have at least four amino acid residues, fragments of SEQ ID NO:73 that have at least four amino acid residues, fragments of SEQ ID NO:74 that have at least four amino acid residues, fragments of SEQ ID NO:75 that have at least four amino acid residues, and fragments of SEQ ID NO:76 that have at least four amino acid residues. In such embodiments, the peptides may further comprise additional amino acid residues.

According to some embodiments of the present invention, peptides comprise amino acid sequences selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

According to some embodiments of the present invention, peptides consist of amino acid sequences selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID

NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

In some embodiments, the peptides are conformationally restricted such as those which are cyclicized, circularized or otherwise restricted by peptide and/or non-peptide bonds to limit conformational variation and/or to increase stability and/or half-life of the peptides. In some embodiments, peptides are provided as linear peptides.

In some embodiments, peptides of the present invention comprise one or more D amino acids. As used herein, the term "D amino acid peptides" is meant to refer to peptides according to the present invention which comprise at least one and preferably a plurality of D amino acids. D amino acid peptides consist of 4-25 amino acids. D amino acid peptides retain the biological activity of the peptides of the invention that consist of L amino acids, i.e. D amino acid peptides inhibit TNFα. In some embodiments, the use of D amino acid peptides is desirable as they are less vulnerable to degradation and therefore have a longer half life.

As used herein, the term "derivatives" refers to peptides of the invention which have the amino terminal and/or the carboxy terminal blocked, particularly those in which the amino group of the N terminal residue is acetylated and/or the carboxy group of the C terminal residue is amidated. Peptides that comprise an amino acid sequence which consists of 4 to 25 amino acids and which comprise at least a four amino acid residue fragment of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID

NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76 include derivatives. Peptides that consist of amino acid sequences selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76 may also be derivatized.

In some preferred embodiments, the peptides of the invention are selected from the group consisting of: SEQ ID NO:1 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:2 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:3 in which the carboxy terminal serine is serine amide; SEQ ID NO:4 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:5 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:6 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:7 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:8 in which the carboxy terminal valine is valine

amide; SEQ ID NO:9 in which the carboxy terminal tryptophan is tryptophan amide; SEQ ID NO:10 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide; SEQ ID NO:12 in which the amino terminal leucine is acetyl leucine and the carboxy terminal valine is valine amide; SEQ ID NO:13 in which the amino terminal alanine is acetyl alanine and the carboxy terminal serine is serine amide; SEQ ID NO:14 in which the carboxy terminal serine is serine amide; SEQ ID NO:15 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:16 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:17 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:18 in which the carboxy terminal serine is serine amide; SEQ ID NO:19 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:20; SEQ ID NO:21 in which the carboxy terminal valine is valine amide; SEQ ID NO:22 in which the carboxy terminal serine is serine amide; SEQ ID NO:23 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:25 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:26 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:27 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:28 in which the carboxy terminal methionine is methionine amide; SEQ ID NO:29 in which the carboxy terminal serine is serine amide; SEQ ID NO:30 in which the carboxy terminal serine is serine amide; SEQ ID NO:31 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:32 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:33 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:34 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:35 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:36 in which the carboxy terminal proline is proline amide; SEQ ID NO:37 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:38 in which the carboxy terminal glycine is

glycine amide; SEQ ID NO:39 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:40 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:41 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:42 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:43 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:44 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:45 in which the carboxy terminal proline is proline amide; SEQ ID NO:46 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:47 in which the carboxy terminal valine is valine amide; SEQ ID NO:48 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:49 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:50 in which the carboxy terminal serine is serine amide; SEQ ID NO:51 in which the carboxy terminal proline is proline amide; SEQ ID NO:52 in which the carboxy terminal serine is serine amide; SEQ ID NO:53 in which the carboxy terminal proline is proline amide; SEQ ID NO:54 in which the carboxy terminal valine is valine amide; SEQ ID NO:55 in which the carboxy terminal histidine is histidine amide; SEQ ID NO:56 in which the carboxy terminal proline is proline amide; SEQ ID NO:57 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:58 in which the carboxy terminal serine is serine amide; SEQ ID NO:59 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:60 in which the carboxy terminal proline is proline amide; SEQ ID NO:61 in which the carboxy terminal proline is proline amide; SEQ ID NO:62 in which the carboxy terminal proline is proline amide, SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:64 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal arginine is arginine amide; SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide; SEQ ID NO:66 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:67 in which the amino terminal threonine is acetyl threonine and the

carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide; SEQ ID NO:69 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:70 in which the amino terminal isoleucine is acetyl isoleucine and the carboxy terminal tryptophan is tryptophan amide; and SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide, SEQ ID NO:72 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:74 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:75 in which the carboxy terminal glutamine is glutamine amide; and SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide.

Contemplated equivalents include conservative analogs and mimetics. Conservative analogs inhibit TNFα in the same manner as the peptides of the invention. By interacting with TNFα in such a way and thereby inhibiting TNFα activity, conservative analogs perform essentially the same function by essentially the same means to achieve essentially the same result as the peptides of the invention. In addition to conservative analogs, the present invention contemplates compounds which display substantially the same surface as the peptides of the invention. As used herein, the term "mimetics" is meant to refer to compounds that are not peptides but that comprise a similar surface as the peptides of the invention and can thus interact with the TNF receptor in a similar fashion as the peptides of the invention. Mimetics inhibit TNFα by interacting with TNFα in the same manner as the peptides of the invention. By providing a similar surface involved in intermolecular interactions, mimetics perform essentially the same function by essentially the same means to achieve essentially the same result as the peptides of the invention.

Peptides of the invention, including D amino acid peptides, may be prepared using the solid-phase synthetic

technique initially described by Merrifield, in *J. Am. Chem. Soc.*, 15:2149-2154 (1963). Other peptide synthesis techniques may be found, for example, in M. Bodanszky *et al.*, (1976) *Peptide Synthesis*, John Wiley & Sons, 2d Ed.; Kent and Clark-Lewis in *Synthetic Peptides in Biology and Medicine*, p. 295-358, eds. Alitalo, K., *et al.* Science Publishers, (Amsterdam, 1985); as well as other reference works known to those skilled in the art. A summary of peptide synthesis techniques may be found in J. Stuart and J.D. Young, *Solid Phase Peptide Synthelia*, Pierce Chemical Company, Rockford, IL (1984), which is incorporated herein by reference. The synthesis of peptides by solution methods may also be used, as described in *The Proteins*, Vol. II, 3d Ed., p. 105-237, Neurath, H. et al., Eds., Academic Press, New York, NY (1976). Appropriate protective groups for use in such syntheses will be found in the above texts, as well as in J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, New York, NY (1973), which is incorporated herein by reference. In general, these synthetic methods involve the sequential addition of one or more amino acid residues or suitable protected amino acid residues to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid residue is protected by a suitable, selectively removable protecting group. A different, selectively removable protecting group is utilized for amino acids containing a reactive side group, such as lysine.

Block synthesis techniques may also be applied to both the solid phase and solution methods of peptide synthesis. Rather than sequential addition of single amino acid residues, preformed blocks comprising two or more amino acid residues in sequence are used as either starting subunits or subsequently added units rather than single amino acid residues.

Using a solid phase synthesis as an example, the protected or derivatized amino acid is attached to an inert solid support through its unprotected carboxyl or amino group. The protecting group of the amino or carboxyl group is then selectively removed and the next amino acid in the sequence

having the complementary (amino or carboxyl) group suitably protected is admixed and reacted with the residue already attached to the solid support. The protecting group of the amino or carboxyl group is then removed from this newly added amino acid residue, and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining terminal and side group protecting groups (and solid support) are removed sequentially or concurrently, to provide the final peptide. The peptide of the invention are preferably devoid of benzylated or methylbenzylated amino acids. Such protecting group moieties may be used in the course of synthesis, but they are removed before the peptides are used. Additional reactions may be necessary, as described elsewhere, to form intramolecular linkages to restrain conformation.

In order to determine whether a peptide inhibits TNFα, one or more of several assays may be performed. Included among these are assays which measure the ability a TNFα inhibitor candidate, i.e. a test compound, to inhibit TNFα from binding to a fusion protein that is composed of a TNF receptor or a TNFα-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit TNFα from binding to an isolated TNF receptor is measured. Other assays include those which the ability of a TNFα inhibitor candidate, i.e. a test compound, to inhibit TNFα activity when TNFα is contacted with cells that react to the presence of TNFα. For example, TNFα is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit TNFα cytotoxicity.

There are numerous other assays which can be used to determine a test compound's ability to inhibit TNFα. In some assays, specific non-lethal effects of TNFα on some cells is used as an end point to evaluate the TNFα inhibitory activity of a test compound. Known effects of TNFα on fibroblast cells include effects on mitogenesis, IL-6 secretion and HLA class II antigen induction. Comparisons can be made between TNFα's

effect on fibroblasts in the presence or absence of a test compound using these detectable phenotypic changes as endpoints. Similarly, known effects of TNFα on monocyte cells include effects on secretion of cytokines such as GMCSF, IL-6 and IL-8. Comparisons can be made between TNFα's effect on cytokine secretion by monocytes in the presence or absence of a test compound. Additionally, TNFα is known to have effects on secretion of cytokine by endothelial cells and similar assays may be designed and performed. Further, TNFα is also known to effect adhesion molecule induction, ICAM-1, E-selectin, VCAM and tissue factor production in endothelial cells. Comparisons can be made between TNFα's effect on endothelial cells in the presence or absence of a test compound using these detectable phenotypic changes as endpoints as well. Likewise, TNFα is known to effect neutrophils in specific ways. Comparisons can be made between TNFα's effect on neutrophils in the presence or absence of a test compound using activation, priming, degranulation and superoxide production as detectable endpoints for evaluation of TNFα inhibitory activity. These and other assays are well known to those having ordinary skill in the art. Such assays may be designed and performed routinely form readily available starting materials.

The TNFα inhibitors according to the invention are useful for treating a vertebrate having a pathology or condition associated with levels of a substance reactive with a TNF receptor, in particular TNFα, in excess of the levels present in a normal healthy subject. Such pathologies include, but are not limited to: sepsis syndrome, including cachexia; circulatory collapse and shock resulting from acute or chronic bacterial infection; acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections; acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus and rheumatoid arthritis; alcohol-induced hepatitis; chronic inflammatory pathologies such as sarcoidosis and Crohn's pathology; vascular inflammatory pathologies such as disseminated intravascular coagulation;

graft-versus-host pathology; Rawasaki's pathology; and malignant pathologies involving TNFα-secreting tumors.

Such treatment comprises administering a single or multiple doses of the compounds of the invention. Preferred for human pharmaceutical use are pharmaceutical compositions that comprise the compounds of the present invention in combination with a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions of the present invention may be administered by any means that enables the active agent to reach the agent's site of action in the body of a mammal. In the case of the peptides of the invention, the primary focus is the ability to reach and bind with TNFα. Because proteins are subject to being digested when administered orally, parenteral administration, i.e., intravenous, subcutaneous, intramuscular, would ordinarily be used to optimize absorption. In some preferred embodiments, pharmaceutical compositions which comprise the compounds of the present invention are administered intravenously or subcutaneously.

Pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 0.001 to 1 grams per kilogram of body weight, in some embodiments about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily dosages are in the range of 0.5 to 50 milligrams per kilogram of body weight, and preferably 1 to 10 milligrams per kilogram per day. In some embodiments, the pharmaceutical compositions are given

in divided doses 1 to 6 times a day or in sustained release form is effective to obtain desired results.

Dosage forms (composition) suitable for internal administration generally contain from about 1 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95 by weight based on the total weight of the composition.

For parenteral administration, the TNFα inhibitor can be formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The vehicle or lyophilized powder may contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by commonly used techniques.

Suitable pharmaceutical carriers are described in the most recent edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For example, a parenteral composition suitable for administration by injection is prepared by dissolving 1.5% by weight of active ingredient in 0.9% sodium chloride solution.

The present invention also provides the peptide-based inhibitors of TNFα including fragments, derivatives, and mimetics thereof which are detectably labeled, as described below, for use in diagnostic methods for detecting TNFα in patients known to be or suspected of having a TNFα-mediated condition. Identification of peptides useful as diagnostic reagents may be performed routinely.

The detectably labelled molecules of the present invention are useful for immunoassays which detect or quantitate TNFα in a sample. An immunoassay for TNFα typically comprises incubating a biological sample in the presence of a detectably labeled high affinity molecule of the present

invention capable of selectively binding to TNF, and detecting the labeled molecules which is bound in a sample. Various clinical immunoassay procedures are described in *Immunoassays for the 80's*, A. Voller et al., Eds., University Park, 1981.

Thus, in this aspect of the invention, the molecule or a biological sample may be added to nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled TNFα-specific antibody. The solid phase support may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support may then be detected by conventional means.

By "solid phase support" or "carrier" is intended any support capable of binding TNFα proteins or molecules of the present invention. Well-known supports or carriers, include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to TNFα or an anti-TNFα antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding TNFα or compounds of the invention, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of anti-TNFα compound may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

One of the ways in which the TNFα-specific molecule can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA), or enzyme-linked immunosorbent assay (ELISA). This enzyme, when subsequently exposed to its substrate, will react with the substrate generating a chemical moiety which can be detected, for example, by spectrophotometric, fluorometric or by visual means. Enzymes which can be used to detectably label the TNFα-specific molecules of the present invention include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. By radioactively labeling the TNFα-specific molecules, it is possible to detect TNFα through the use of a radioimmunoassay (RIA) (see, for example, Work, T.S., et al., *Laboratory Techniques and Biochemistry in Molecular Biology*, North Holland Publishing Company, N.Y., 1978. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography. Isotopes which are particularly useful for the purpose of the present invention are: ^{3}H, ^{125}I, ^{131}I, ^{35}S, ^{14}C, and, preferably, ^{125}I.

It is also possible to label the TNFα-specific molecules with a fluorescent compound. When the fluorescent labeled compound is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labelling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

The TNFα-specific molecules can also be detectably labeled using fluorescence-emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the TNFα-specific molecule using such metal chelating groups

as diethylenetriaminepentaacetic acid (DTPA) or ethylenediamine-tetraacetic acid (EDTA).

The TNFα-specific molecules also can be detectably labeled by coupling to a chemiluminescent compound. The presence of the chemiluminescently labeled compound is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the TNFα-specific molecule, fragment or derivative of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin. Detection of the TNFα-specific compound, fragment or derivative may be accomplished by a scintillation counter, for example, if the detectable label is a radioactive gamma emitter, or by a fluorometer, for example, if the label is a fluorescent material. In the case of an enzyme label, the detection can be accomplished by colorometric methods which employ a substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

For the purposes of the present invention, the TNFα which is detected by the above assays may be present in a biological sample. Any sample containing TNFα can be used. Preferably, the sample is a biological fluid such as, for example, blood, serum, lymph, urine, inflammatory exudate, cerebrospinal fluid, amniotic fluid, a tissue extract or homogenate, and the like. However, the invention is not limited to assays using only these samples, it being possible for one of ordinary skill in

the art to determine suitable conditions which allow the use of other samples.

In situ detection may be accomplished by removing a histological specimen from a patient, and providing the combination of labeled antibodies of the present invention to such a specimen. The peptide is preferably provided by applying or by overlaying the labeled molecule (or fragment) to a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of TNFα but also the distribution of TNFα in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

The peptide, fragment or derivative of the present invention may be adapted for utilization in an immunometric assay, also known as a "two-site" or "sandwich" assay. In a typical immunometric assay, a quantity of unlabeled peptide (or fragment of the peptide) is bound to a solid support that is insoluble in the fluid being tested and a quantity of detectably labeled soluble antibody is added to permit detection and/or quantitation of the ternary complex formed between solid-phase peptide, TNFα, and labeled anti-TNFα antibody.

Typical and preferred immunometric assays include "forward" assays in which the peptide of the invention bound to the solid phase is first contacted with the sample being tested to extract the TNFα from the sample by formation of a binary solid phase peptide-TNFα complex. After a suitable incubation period, the solid support is washed to remove the residue of the fluid sample, including unreacted TNFα, if any, and then contacted with the solution containing a known quantity of labeled peptide (which functions as a "reporter molecule"). After a second incubation period to permit the labeled peptide to complex with the TNFα bound to the solid support through the unlabeled peptide, the solid support is washed a second time to remove the unreacted labeled peptide. This type of forward

sandwich assay may be a simple "yes/no" assay to determine whether TNFα is present or may be made quantitative by comparing the measure of labeled peptide with that obtained for a standard sample containing known quantities of TNFα. Such "two-site" or "sandwich" assays are described by Wide, *Radioimmune Assay Method*, Kirkham, Ed., E. & S. Livingstone, Edinburgh, 1970, pp. 199-206).

Other type of "sandwich" assays, which may also be useful with TNFα, are the so-called' "simultaneous" and "reverse" assays. A simultaneous assay involves a single incubation step wherein the peptide bound to the solid support and labeled peptide are both added to the sample being tested at the same time. After the incubation is completed, the solid support is washed to remove the residue of fluid sample and uncomplexed labeled peptide. The presence of labeled peptide associated with the solid support is then determined as it would be in a conventional "forward" sandwich assay.

In the "reverse" assay, stepwise addition first of a solution of labeled peptide to the fluid sample followed by the addition of unlabeled antibody bound to a solid support after a suitable incubation period, is utilized. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labeled peptide. The determination of labeled peptide associated with a solid support is then determined as in the "simultaneous" and "forward" assays. In one embodiment, a combination of peptide of the present invention specific for separate epitopes may be used to construct a sensitive three-site immunoradiometric assay.

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EXAMPLES

Example 1 Leucyl-tyrosyl-asparaginyl-aspartyl-alanyl-prolyl-glycyl-prolyl-glycyl-glutaminyl-aspartyl-threonyl-aspartyl-alanyl-arginine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.64 g.

The peptide was cleaved from the resin (1.6 g) using 16 mL of HF and 1.6 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 720 mg of crude peptide.

The crude peptide (720 mg) was dissolved in 150 mL of 50% acetic acid and purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 10-45% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 72 mg of white solid.

Amino acid analysis: Ala 2.03 (2), Arg 1.04 (1), Asx 3.94 (4), Glx 1.05 (1), Gly 2.08 (2), Leu 0.96 (1), Pro 2.00 (2), Thr 0.90 (1), Tyr 0.90 (1). FAB/MS: MH^+ 1590.2

Example 2 Glycyl-prolyl-glycyl-glutaminyl-aspartyl-threonyl-aspartyl-alanyl-arginyl-glutamyl-alanyl-glutamyl-seryl-glycyl-serine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.89 g.

The peptide was cleaved from the resin (1.89 g) using 19 mL of HF and 1.9 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 960 mg of crude peptide.

The crude peptide (960 mg) was dissolved in 80 mL at 30% acetic acid and purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 10-30% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per

min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 340 mg of white solid.

Amino acid analysis: Ala 2.19 (2), Arg 1.01 (1), Asx 2.00 (2), Glx 2.79 (3), Gly 3.02 (3), Pro 0.99 (1), Ser 1.53 (2), Thr 0.89 (1). FAB/MS: MH^+ 1477.7

Example 3 Glutaminyl-aspartyl-threonyl-aspartyl-alanyl-arginyl-glutamyl-alanyl-glutamyl-seryl-glycyl-seryl-phenylalanyl-threonyl-alanine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.91 g.

The peptide was cleaved from the resin (1.91 g) using 19 mL of HF and 1.9 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 50% trifluoroacetic acid in methylene chloride to give 660 mg of crude peptide.

The crude peptide (660 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 10-45% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 151 mg.

Amino acid analysis: Ala 3.20 (3), Arg 0.92 (1), Asx 1.63 (2), Glx 2.88 (3), Gly 1.19 (1), Phe 1.17 (1), Ser 2.05 (2), Thr 1.82 (2). FAB/MS: MH^+ 1586.1

Example 4 Glutamyl-alanyl-glutamyl-seryl-glycyl-seryl-phenylalanyl-threonyl-alanyl-seryl-glutamyl-asparaginyl-histidyl-leucyl-arginine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.12 g.

The peptide was cleaved from the resin (2.1 g) using 21 mL of HF and 2.1 mL of anisole for 60 min at 0°C. The resin

was washed with ether and the peptide extracted with 50% trifluoroacetic acid in methylene chloride to give 783 mg of crude peptide.

The crude peptide (783 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 10-50% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 133 mg.

Amino acid analysis: Ala 2.16 (2), Arg 1.01 (1), Asx 1.01 (1), Glx 2.86 (3), Gly 1.05 (1), His 0.93 (1), Leu 0.95 (1), Phe 1.03 (1), Ser 2.66 (3), Thr 0.97 (1). FAB/MS: MH^+ 1636.2

Example 5 Aspartyl-threonyl-valyl-alanyl-glycyl-alanyl-arginyl-lysyl-asparaginyl-glutaminyl-tyrosyl-arginyl-histidyl-tyrosyl-tryptophan amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.26 g.

The peptide was cleaved from the resin (2.1 g) using 21 mL of HF and 2.1 mL anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 50% trifluoroacetic acid/methylene chloride to give 1.19 g of crude peptide.

The crude peptide (1.1 g) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 10-40% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per min. Semipure fractions were pooled and rechromatographed (same column) with a 15-40% gradient of 80% ethanol in 0.1% trifluoroacetic acid. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 172 mg.

Amino acid analysis: Ala 2.12 (2), Arg 2.13 (2), Asx 2.12 (2), Glx 1.08 (1), Gly 1.08 (1), His 1.37 (1), Lys 1.07 (1), Thr 0.63 (1), Trp 0.23 (1), Tyr 2.02 (2), Val 0.79 (1). FAB/MS: MH^+ 1866.2

Example 6 Acetyl-glutaminyl-tyrosyl-arginyl-histidyl-tyrosyl-tryptophyl-seryl-glutamyl-asparaginyl-leucyl-phenylalanyl-glutaminyl-alanyl-phenylalanyl-asparagine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-methyl benzhydrylamine resin (0.58 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.51 g.

The peptide was cleaved from the resin (1.5 g) using 15 mL of HF and 1.5 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 780 mg of crude peptide.

The crude peptide (780 mg) was dissolved in 110 mL of 80% acetic acid and purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 20-80% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 235.3 mg of white solid.

Amino acid analysis: Ala 1.25 (1), Arg 0.84 (1), Asx 2.60 (2), Glx 2.68 (3), His 0.79 (1), Leu 1.03 (1), Phe 2.05 (2), Ser 0.62 (1),Trp 0.98 (1) Tyr 1.76 (2). FAB/MS: MH^+ 2046.8

Example 7 Acetyl-leucyl-phenylalanyl-glutaminyl-alanyl-phenylalanyl-asparaginyl-alanyl-seryl-leucyl-alanyl-leucyl-asparaginyl-glycyl-threonyl-valine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.55 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.583 g.

The peptide was cleaved from the resin (1.385 g) using 14 mL of HF and 1.4 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with a 1:1 solution of trifluoroacetic acid/methylene chloride to give 839 mg of crude peptide.

The crude peptide (200 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 40-80% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 14 mg.

Amino acid analysis: Ala 3.05 (3), Asx 2.01 (2), Glx 0.96 (1), Gly 0.97 (1), Leu 3.11 (3), Phe 2.02 (2), Ser 0.80 (1), Thr 0.73 (1), Val 0.88 (1). FAB/MS: MH^+ 1607.6

Example 8 Acetyl-alanyl-phenylalanyl-asparaginyl-alanyl-seryl-leucyl-alanyl-leucyl-asparaginyl-glycyl-threonyl-valyl-histidyl-leucyl-serine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.55, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.441 g.

The peptide was cleaved from the resin (1.333 g) using 13 mL of HF and 1.3 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with a 1:1 solution of trifluoroacetic acid/methylene chloride to give 585 mg of crude peptide.

The crude peptide (500 mg) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 20-60% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 34 mg.

Amino acid analysis: Ala 3.08 (3), Asx 2.03 (2), Gly 0.99 (1), His 0.97 (1), Leu 3.38 (3), Phe 0.88 (1), Ser 1.79 (2), Thr 0.74 (1), Val 0.67 (1). FAB/MS: MH^+ 1557.6

Example 9 Glutaminyl-glutamyl-lysyl-glutaminyl-asparaginyl-threonyl-valyl-alanyl-threonyl-alanyl-histidyl-alanyl-glycyl-phenylalanyl-phenylalanyl-leucyl-arginyl-glutamyl-asparaginyl-glutamic acid amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.46 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.724 g.

The peptide was cleaved from the resin (1.724 g) using 17 mL of HF and 1.7 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with a 1:1 solution of trifluoroacetic acid/methylene chloride to give 976 mg of crude peptide.

The crude peptide (610 mg) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 25-70% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 60 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 127 mg of peptide that is a mixture of N-terminal glutamine and pyroglutamine.

Amino acid analysis: Ala 3.42 (3), Arg 1.22 (1), Asx 1.92 (2), Glx 4.10 (5), Gly 1.21 (1), His 1.22 (1), Leu 1.24 (1), Lys 0.56 (1), Phe 2.47 (2), Thr 1.56 (2), Val 0.64 (1). FAB/MS: MH^+ 2273.4

Example 10 Lysyl-glutaminyl-asparaginyl-threonyl-valyl-alanyl-threonyl-alanyl-histidyl-alanyl-glycyl-phenylalanyl-phenylalanyl-leucyl-arginine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (588 mg, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.67 g.

The peptide was cleaved from the resin (1.67 g) using 17 mL of HF and 1.7 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 30% acetic acid to give 743 mg of crude peptide.

The crude peptide (390 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 23-35% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 90 mg of pure peptide.

Amino acid analysis: Ala 3.18 (3), Arg 1.06 (1), Asx 1.06 (1), Glx 0.93 (1), Gly 1.09 (1), His 1.10 (1), Leu 1.01 (1), Lys 1.02 (1), Phe 1.88 (2), Thr 1.45, Val 0.68 (1). FAB/MS: MH^+ 1661.6

Example 11 Arginyl-glutamyl-asparaginyl-glutamyl-cysteinyl-valyl-seryl-cysteinyl-seryl-asparaginyl-cysteinyl-lysyl-lysyl-seryl-leucyl-glutamyl-cysteinyl-threonyl-lysyl-leucine

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. Boc-Leu-PAM resin (667 mg, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.7 g.

The peptide was cleaved from the resin (2.7 g) using 27 mL of HF and 2.7 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 50% Trifluoroacetic acid in Methylene chloride to give 652 mg of crude peptide.

The crude Acm-Cys protected peptide (652 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 10-50% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 182 mg. The crude linear peptide (79 mg, 0.031 mmol) was deprotected with $Hg(OAc)_2$ (3.94 mg, 0.124 mmol) in 35 mL of 30% acetic acid at room temperature for 1 hr. The reaction was quenched with dithiothrietol (48 mg, 0.31 mmol). The crude linear peptide was purified on a Vydac C-18 (10μ, 2.5 x 25 cm) column using a 10-50% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 60 min at 10 mL/min. Fractions were analyzed by HPLC and pure fractions were pooled to give 14 mg.

Amino acid analysis: Arg 1.09 (1), Asx 2.29 (2), Glx 3.37 (3), Leu 2.25 (2), Lys 3.37 (3), Ser 1.53 (3), Thr 1.29 (1), Val 1.10 (1). FAB/MS: MH^+ 2277.5 (MNa^+ - $4H^+$)

Example 12 Seryl-leucyl-glutamyl-alanyl-threonyl-lysyl-leucyl-alanyl-leucyl-prolyl-glutaminyl-isoleucyl-glutamyl-asparaginyl-valine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-methyl benzhydrylamine resin (588 mg, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.66 mg.

The peptide was cleaved from the resin (1.66 g) using 17 mL of HF and 1.7 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 20% acetic acid to give 815 mg of crude peptide.

The crude peptide (305 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 37-60% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 133 mg of pure peptide.

Amino acid analysis: Ala 2.12 (2), Asx 1.01 (1), Glx 2.94 (3), Ile 0.96 (1), Leu 2.93 (3), Lys 1.01 (1), Pro 1.00 (1), Ser 0.71 (1), Thr 0.86 (1), Val 1.02 (1). FAB/MS: MH^+ 1626.7

Example 13 Leucyl-alanyl-leucyl-prolyl-glutaminyl-isoleucyl-glutamyl-asparaginyl-valyl-lysyl-glycyl-threonyl-glutamyl-aspartyl-serine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (588 mg, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.87 g.

The peptide was cleaved from the resin (1.87 g) using 19 mL of HF and 1.9 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 30% acetic acid to give 943 mg of crude peptide.

The crude peptide (460 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 32-45% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 260 mg of pure peptide.

Amino acid analysis: Ala 1.08 (1), Asx 2.13 (2), Glx 2.93 (3), Gly 1.06 (1), Ile 0.95 (1), Leu 2.11 (2), Lys 0.86 (1), Pro 1.04 (1), Ser 0.76 (1), Thr 0.96 (1), Val 0.85 (1). FAB/MS: MH^+ 1614.9

Example 14 Prolyl-glutaminyl-isoleucyl-glutamyl-asparaginyl-valyl-lysyl-glycyl-threonyl-glutamyl-asparaginyl-seryl-glycyl-threonyl-threonine amide

The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (588 mg, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.88 g.

The peptide was cleaved from the resin (1.88 g) using 19 mL of HF and 1.9 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 30% acetic acid to give 790 mg of crude peptide.

The crude peptide (502 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 12-23% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 227 mg of pure peptide.

Amino acid analysis: Asx 2.10 (2), Glx 2.92 (3), Gly 2.10 (2), Ile 0.98 (1), Lys 0.95 (1), Pro 1.03 (1), Ser 0.72 (1), Thr 2.48 (3), Val 0.92 (1). FAB/MS: MH^+ 1577.4

Example 15 Acetyl-leucyl-isoleucyl-lysyl-tyrosyl-alanyl-seryl-glutaminyl-seryl-methionyl-seryl-glycyl-isoleucine-amide

This peptide is a derivative of SEQ ID NO:63 having the same amino acid sequence as SEQ ID NO:63 except that in this derivative, the N terminal leucine residue is blocked, forming acetyl-leucine and the C terminal isoleucine is blocked, forming isoleucine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.55 g.

The peptide was cleaved from the resin (1.5 g) using 15 mL of HF, 2-mercaptopyridine (1.0 g) and 1.5 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 610 mg of crude peptide.

The crude peptide (600 mg) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a a) 0-25%; b) 25-65%% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over a) 15 min; b) 45 min at a flow rate of 120 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 195 mg of white solid.

Amino acid analysis: Ala 1.08 (1), Glx 0.98 (1), Gly 1.03 (1), Ile 1.86 (2), Leu 1.02 (1), Lys 0.89 (1), Met 0.64 (1), Ser 2.27 (3), Tyr 0.83 (1). FAB/MS: MH^+ 1339.5

Example 16 Acetyl-phenylalanyl-seryl-asparaginyl-histidyl-tryptophyl-methionyl-asparaginyl-tryptophyl-valyl-arginine-amide

This peptide is a derivative of SEQ ID NO:64 having the same amino acid sequence as SEQ ID NO:64 except that in this derivative, the N terminal phenylalanine residue is blocked, forming acetyl-phenylalanine and the C terminal arginine is blocked, forming arginine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.5 g.

The peptide was cleaved from the resin (1.5 g) using 15 mL of HF, dithiothreitol (1.0 g) and anisole (1.5 mL) for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 1.03 g of crude peptide. The crude peptide was dissolved in dimethylformamide (100 mL), diluted with water (20 mL), stirred with 2 mL of piperidine over 60 min at room temperature then evaporated to dryness (1.7 g, yellow oil).

The crude peptide (about 1.5 g) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a a) 0-25%; b) 25-65% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over a) 15 min; b) 45 min at a flow rate of 120 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 145 mg of white solid.

Amino acid analysis: Arg 1.03 (1), Asx 1.51 (2), His 1.03 (1), Met 0.92 (1), Phe 1.03 (1), Ser 0.81 (1), Trp 0.67 (2), Val 0.99 (1). FAB/MS: MH^+ 1417.4

Example 17 Acetyl-tyrosyl-alanyl-glutamyl-seryl-valyl-lysyl-glycyl-arginyl-phenylalanyl-threonyl-isoleucyl-seryl-arginyl-aspartyl-aspartyl-seryl-lysyl-seryl-alanyl-valyl-tyrosyl-leucine-amide

This peptide is a derivative of SEQ ID NO:65 having the same amino acid sequence as SEQ ID NO:65 except that in this derivative, the N terminal tyrosine residue is blocked, forming acetyl-tyrosine and the C terminal leucine is blocked, forming leucine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.46 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.730 g.

The peptide was cleaved from the resin (1.730 g) using 17 mL of HF and 1.7 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with a 1:1 solution of trifluoroacetic acid/methylene chloride to give 1.220 g of crude peptide.

The crude peptide (795 mg) was purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 20-60% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 175 mg.

Amino acid analysis: Ala 1.99 (2), Arg 1.83 (1), Asx 2.48 (2), Glx 1.20 (1), Gly 0.91 (1), Ile 0.91 (1), Leu 0.99 (1), Lys 1.74 (2), Phe 0.94 (1), Ser 2.04 (4), Thr 0.57 (1), Tyr 1.71 (2), Val 1.77 (2).

Example 19 Arginyl-glutaminyl-seryl-prolyl-glutamyl-lysyl-glycyl-leucyl-glutamyl-tryptophyl-valyl-alanyl-glutamyl-isoleucyl-arginyl-seryl-lysyl-seryl-isoleucine-amide

This peptide is a derivative of SEQ ID NO:66 having the same amino acid sequence as SEQ ID NO:66 except that in this derivative, the C terminal isoleucine is blocked, forming

isoleucine amide. The peptide was prepared on an ABI Model 431A peptide synthesizer using version 1.12 of the standard Boc software. The synthesis was done on 4 methylbenzyhydrylamine resin (Bachem 0.637 g, 0.51 mmol). The final weight of the dried resin was 2.217 g.

The peptide was cleaved from the resin (2.059 g) using anisole (2.0 mL) and HF (18 mL) at 0° C for 60 min. The peptide and resin were precipitated with ether and dried. The peptide was extracted with a mixture of trifluoroacetic acid and dichloromethane (1/1, 100 mL). The solvents were removed *in vacuo* to give an oil, and the oil triturated with ether to give the crude peptide as a gummy off-white solid (0.56 g). The solid was dissolved in 30 mL of 2,2,2-trifluoroethanol and treated with 75 mL of 2% piperidine in water for 1 hr at room temperature.

The peptide was purified on the Vydac C-18 column (15μm, 2.2 x 25 cm), eluting with a gradient of acetonitrile in 0.1% trifluoroacetic acid (24% to 40% acetonitrile over 50 min at 5 mL/min). Fractions containing the purified peptide were combined and lyophilized to give 60 mg of a white solid.

Amino acid analysis: Ala 1.04 (1), Arg 2.07 (2), Glx 3.86 (4) Gly 1.04 (1), Ile 2.04 (2), Leu 1.12 (1.10), Lys 2.08 (2), Pro 0.74 (1), Ser 2.23 (3), Trp 0.0 (1), Val 1.05 (1.0). FAB/MS: MH^+ 2213

Example 20 Acetyl-threonyl-aspartyl-leucyl-arginyl-threonyl-glutamyl-aspartyl-threonyl-glycyl-valyl-tyrosyl-tyrosyl-cysteinyl-seryl-arginyl-asparaginyl-tyrosyl-tyrosyl-glycyl-seryl-threonyl-tyrosine-amide

This peptide is a derivative of SEQ ID NO:67 having the same amino acid sequence as SEQ ID NO:67 except that in this derivative, the N terminal threonine residue is blocked, forming acetyl-threonine and the C terminal tyrosine is blocked, forming tyrosine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625

g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.473 g.

The peptide was cleaved from the resin (2.267 g) using 18 mL of HF and 2 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with a 1:1 solution of trifluoroacetic acid/methylene chloride to give 1.07 g of crude peptide.

The crude peptide (1.07 g) was purified on a Vydac C-18 column (15μ, 2.2 x 25 cm) eluting with a 15-80% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 415 min at a flow rate of 5 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 100 mg.

Amino acid analysis: Arg 2.03 (2), Asx 3.09 (3), Cys 0.64 (1), Glx 1.07 (1), Gly 2.14 (2), Leu 1.0 (1), Ser 1.55 (2), Thr 3.48 (4), Tyr 4.67 (5), Val 1.09 (1).

Example 21 Acetyl-aspartyl-isoleucyl-leucyl-leucyl-threonyl-glutaminyl-seryl-prolyl-alanyl-isoleucyl-leucyl-seryl-valyl-seryl-prolyl-glycyl-glutamyl-arginyl-valyl-seryl-phenylalanyl-serine-amide

This peptide is a derivative of SEQ ID NO:68 having the same amino acid sequence as SEQ ID NO:68 except that in this derivative, the N terminal aspartic acid residue is blocked, forming acetyl-aspartic acid and the C terminal serine is blocked, forming serine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.0 g.

The peptide was cleaved from the resin (2 g) using 20 mL of HF and 2 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 1.06 g of crude peptide.

The crude peptide (0.6 g) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 0-30% over 10 min and 30-60% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 50 min at a flow rate of 120 mL per min. Fractions

were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 182 mg of white solid.

Amino acid analysis: Ala 1.13 (1), Arg 0.98 (1), Asx 0.93 (1), Glx 1.93 (2), Gly 1.06 (1), Ile 1.87 (2), Leu 2.96 (3), Phe 1.03 (1), Pro 1.95 (2), Ser 3.19 (5), Thr 0.72 (1), Val 2.04 (2). MH^+ 2358.4

Example 22 Acetyl-tyrosyl-tyrosyl-seryl-glutaminyl-glutaminyl-seryl-histidyl-seryl-tryptophyl-prolyl-phenylalanyl-threonyl-phenylalanine-amide

This peptide is a derivative of SEQ ID NO:69 having the same amino acid sequence as SEQ ID NO:69 except that in this derivative, the N terminal tyrosine residue is blocked, forming acetyl-tyrosine and the C terminal phenylalanine is blocked, forming phenylalanine amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 1.87 g.

The peptide was cleaved from the resin (1.8 g) using 18 mL of HF and 1.8 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 592 mg of crude peptide.

The crude peptide (590 mg) was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a a) 0-25%; b) 25-65% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over a) 15 min; b) 45 min at a flow rate of 120 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 155 mg of white solid.

Amino acid analysis: Glx 1.78 (2), His 0.99 (1), Phe 2.00 (2), Pro 1.00 (1), Ser 1.93 (3), Thr 0.82 (1), Trp 0.00 (1), Tyr 1.48 (2). FAB/MS: MH^+ 1719.4

Example 23 Acetyl-isoleucyl-asparaginyl-threonyl-valyl-glutamyl-seryl-glutamyl-aspartyl-isoleucyl-alanyl-aspartyl-tyrosyl-tyrosyl-cysteinyl-glutaminyl-glutaminyl-seryl-histidyl-seryl-tryptophan-amide

This peptide is a derivative of SEQ ID NO:70 having the same amino acid sequence as SEQ ID NO:70 except that in this derivative, the N terminal isoleucine residue is blocked, forming acetyl-isoleucine and the C terminal tryptophan is blocked, forming tryptophan amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard Boc software. 4-Methyl benzhydrylamine resin (0.625 g, 0.5 mmol) was used in the synthesis. The final weight of the resin was 2.2 g.

The peptide was cleaved from the resin (2.2 g) using 22 mL of HF and 2.2 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with trifluoroacetic acid/methylene chloride (1:1, v/v) (3 x 15 mL) to give 1.1 g of crude peptide. The crude peptide (1.0 g) was dissolved in dimethylformamide (40 mL). Water (40 mL) and piperidine (2 mL) were added and stirred for 60 min at room temperature then lyophilized. The resulted solid (approximately 1.8 g) was dissolved in 60% acetic acid (160 mL).

The crude peptide was purified on a Vydac C-18 column (15μ, 10 x 30 cm) eluting with a 0-30% gradient over 10 min and a 30-60% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 50 min at a flow rate of 120 mL per min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 77 mg of white solid.

Amino acid analysis: Ala 1.01 1, Asx 2.99 (3), Cys 0.96 (1), Glx 4.00 (4), His 1.00 (1), Ile 1.79 (2), Ser 2.01 (3), Thr 0.75 (1), Trp ND (1), Tyr 1.79 (2), Val 0.86 (1).

Example 24 Acetyl-phenylalanyl-seryl-asparaginyl-histidyl-tryptophyl-methionyl-asparaginyl-tryptophan-amide

This peptide is a derivative of SEQ ID NO:71 having the same amino acid sequence as SEQ ID NO:71 except that in this derivative, the N terminal phenylalanine residue is blocked, forming acetyl-phenylalanine and the C terminal tryptophan is blocked, forming tryptophan amide. The peptide was prepared on an ABI Model 431A Peptide Synthesizer using version 1.12 of the standard BOC software. 4-Methyl benzhydrylamine resin (0.58 g,

0.5 mmol) was used in the synthesis. The final weight of the resin was 1.3 g.

The peptide was cleaved from the resin (1.3 g) using 13 mL of HF, 1.3 g of 2-mercaptopyridine and 1.3 mL of anisole for 60 min at 0°C. The resin was washed with ether and the peptide extracted with 50% trifluoroacetic acid in methylene chloride to give 1.3 g of crude peptide and salts..

The crude peptide (1.3 g) was first purified on a Vydac C-18 column (15μ, 5 x 25 cm) eluting with a 25-70% gradient of 80% ethanol in 0.1% trifluoroacetic acid over 120 min at a flow rate of 15 mL per min. The semipure peptide (30 mg) was purified on a Vydac C-18 column (10μ, 2.2 x 25 cm) using a 20-60% gradient of 80% acetonitrile in 0.1% trifluoroacetic acid over 60 min at 10 mL/min. Fractions were collected, analyzed by HPLC and pure fractions pooled and lyophilized to give 18 mg.

Amino acid analysis: Asx 2.11 (2), His 1.08 (1), Met 1.37 (1), Phe 1.32 (1), Ser 10.6 (1), Trp 1.12 (2). FAB/MS: MH^+ 1164.2

Example 25 p55 receptor/IgG fusion protein binding assay

In order to screen compounds for their ability to block TNFα binding to the TNF p55 receptor, an assay has been designed using TNFα and a p55/IgG fusion protein in place of monovalent, non-fusion p55 TNF receptor protein. This assay was designed to identify peptides which bind to human TNFα and thereby prevent the capture of the TNFα by a microtiter plate coated with p55-Ig fusion protein. A constant concentration of human TNFα is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound TNFα is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human TNFα bound to the well relative to control wells in which TNFα but no peptide was added.

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 μl/well of p55-Ig fusion protein at 5 μg/ml in 0.01 M sodium phosphate, 0.15 M sodium chloride (PBS) by incubation overnight at 4°C or 2 hours at 37°C. The fusion

protein, which consists of a p55 TNF receptor protein portion and an IgG portion, can be produced as disclosed in U.S. Application Serial Number 08/010,406 filed January 29, 1993 which is incorporated herein by reference. The plate was washed three times with 0.05% Tween-20 in PBS, then blocked, by adding 150 µl/well of assay buffer (10 mM N-2-hydroxyethylpiperazine-N'-3-propanesulfonic acid (HEPES) pH 7.2, containing 0.1% porcine gelatin, 0.1% Tween-80, and 0.01% sodium azide) and continuing incubation for 1 hour at 37°C or at 4°C for 1-7 days.

Lyophilized peptides to be tested were weighed in tared 12 x 75 mm polystyrene tubes and reconstituted to a concentration of 1.2 mM with assay buffer. Each suspension was sonicated in a water bath for 1-5 minutes and vortexed 15-30 seconds to disperse large particles. Serial dilutions of each peptide suspension were prepared using assay buffer in a 96-well polystyrene microtiter plate. Additional wells received Fab fragment of the mouse/human monoclonal anti-human TNFα antibody cA2 (positive control) or assay buffer (negative control). Human recombinant TNFα (Biosource, Camarillo, CA) was added to all wells to give a final TNFα concentration of 25 ng/ml, final peptide concentrations of 1.0, 0.33 and 0.11 mM and a final cA2 Fab concentration of 500 ng/ml. The polystyrene dilution plate was then sealed and incubated 1 hour at room temperature on an orbital mixer set at moderate speed.

Following the sample preincubation, blocker was discarded from the p55-Ig coated plate and blotted dry. Aliquots (50 µl) of each peptide or control were transferred into duplicate wells on the p55-Ig coated plate which was then sealed and incubated 1 hour at 37°C. Duplicate wells containing only assay buffer were included as a plate blank. After incubation the p55-Ig plate was washed three times with 0.05% Tween-20 in PBS.

To detect TNFα captured by the p55-Ig plate, all wells were incubated in succession with polyclonal rabbit anti-human TNFα (Genzyme, Boston, MA; 1:500 in assay buffer, 50 µl/well), biotinylated goat anti-rabbit Ig (H&L) (Vector Laboratories,

Burlingame, CA; 1 μg/ml in assay buffer, 50 μl/well) and streptavidin-alkaline phosphatase conjugate (Pierce, Rockford, IL; 1 μg/ml in assay buffer, 50 μl/well). All incubations were for 1 hour at 37°C and after each incubation the plate was washed three times with 0.05% Tween-20 in PBS. Fifty microliters of alkaline phosphatase substrate solution (alkaline buffer (Sigma, St. Louis, MO) diluted 1:500 in deionized water plus one 5 mg tablet of p-nitrophenyl phosphate (Sigma, St. Louis, MO) per 5 ml of diluted buffer) was added to all wells and incubation continued for 20 minutes at room temperature. Color development was stopped by adding to all wells 50 μl of 3 N sodium hydroxide. The optical density (OD) at 405 nm was measured on a microtiter plate reader (Molecular Devices Vmax plate reader), with the plate blank wells subtracted as background. The activity of each peptide was then expressed as the percent inhibition of TNFα capture by the p55-Ig plate, relative to the amount of TNFα captured in wells containing only assay buffer (negative control), as follows:

% inhibition = 100 - ((mean OD peptide/mean OD negative control) x 100).

The validity of each assay was confirmed by the cA2 Fab positive control which typically inhibited TNFα capture by more than ≥ 75%.

Example 26

The inhibition of binding of TNFα to p55TNFr-IgG chimeric construct was performed as described above using several embodiments of the invention. The peptides were tested at a concentration of 1mM. The following data were generated.

1mM of SEQ ID NO:1 in which the carboxy terminal arginine is arginine amide resulted in 46% inhibition.

1mM of SEQ ID NO:2 in which the carboxy terminal glutamic acid is glutamic acid amide resulted in 62% inhibition.

1mM of SEQ ID NO:3 in which the carboxy terminal serine is serine amide resulted in 53% inhibition.

1mM of SEQ ID NO:4 in which the carboxy terminal alanine is alanine amide resulted in 53% inhibition.

1mM of SEQ ID NO:5 in which the carboxy terminal asparagine is asparagine amide resulted in 58% inhibition.

1mM of SEQ ID NO:6 in which the carboxy terminal arginine is arginine amide resulted in 53% inhibition.

1mM of SEQ ID NO:7 in which the carboxy terminal arginine is arginine amide resulted in 42% inhibition.

1mM of SEQ ID NO:8 in which the carboxy terminal valine is valine amide resulted in 56% inhibition.

1mM of SEQ ID NO:9 in which the carboxy terminal tryptophan is tryptophan amide resulted in 30% inhibition.

1mM of SEQ ID NO:10 in which the carboxy terminal glutamine is glutamine amide resulted in 49% inhibition.

1mM of SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide resulted in 27% inhibition.

1mM of SEQ ID NO:12 in which the amino terminal leucine is acetyl leucine and the carboxy terminal valine is valine amide resulted in 40% inhibition.

1mM of SEQ ID NO:13 in which the amino terminal alanine is acetyl alanine and the carboxy terminal serine is serine amide resulted in 34% inhibition.

1mM of SEQ ID NO:14 in which the carboxy terminal serine is serine amide resulted in 29% inhibition.

1mM of SEQ ID NO:15 in which the carboxy terminal glutamic acid is glutamic acid amide resulted in 48% inhibition.

1mM of SEQ ID NO:16 in which the carboxy terminal arginine is arginine amide resulted in 48% inhibition.

1mM of SEQ ID NO:17 in which the carboxy terminal glutamic acid is glutamic acid amide resulted in 59% inhibition.

1mM of SEQ ID NO:18 in which the carboxy terminal serine is serine amide resulted in 68% inhibition.

1mM of SEQ ID NO:19 in which the carboxy terminal asparagine is asparagine amide resulted in 53% inhibition.

1mM of SEQ ID NO:20 resulted in 26% inhibition.

1mM of SEQ ID NO:21 in which the carboxy terminal valine is valine amide resulted in 50% inhibition.

1mM of SEQ ID NO:22 in which the carboxy terminal serine is serine amide resulted in 34% inhibition.

1mM of SEQ ID NO:23 in which the carboxy terminal threonine is threonine amide resulted in 52% inhibition.

1mM of SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide resulted in 21% inhibition.

1mM of SEQ ID NO:25 in which the carboxy terminal arginine is arginine amide resulted in 69% inhibition.

1mM of SEQ ID NO:26 in which the carboxy terminal tyrosine is tyrosine amide resulted in 71% inhibition.

1mM of SEQ ID NO:27 in which the carboxy terminal threonine is threonine amide resulted in 78% inhibition.

1mM of SEQ ID NO:28 in which the carboxy terminal methionine is methionine amide resulted in 72% inhibition.

1mM of SEQ ID NO:29 in which the carboxy terminal serine is serine amide resulted in 53% inhibition.

1mM of SEQ ID NO:30 in which the carboxy terminal serine is serine amide resulted in 59% inhibition.

1mM of SEQ ID NO:31 in which the carboxy terminal aspartic acid is aspartic acid amide resulted in 68% inhibition.

1mM of SEQ ID NO:32 in which the carboxy terminal glutamic acid is glutamic acid amide resulted in 64% inhibition.

1mM of SEQ ID NO:33 in which the carboxy terminal threonine is threonine amide resulted in 67% inhibition.

1mM of SEQ ID NO:34 in which the carboxy terminal glutamine is glutamine amide resulted in 65% inhibition.

1mM of SEQ ID NO:35 in which the carboxy terminal asparagine is asparagine amide resulted in 72% inhibition.

1mM of SEQ ID NO:36 in which the carboxy terminal proline is proline amide resulted in 77% inhibition.

1mM of SEQ ID NO:37 in which the carboxy terminal leucine is leucine amide resulted in 77% inhibition.

1mM of SEQ ID NO:38 in which the carboxy terminal glycine is glycine amide resulted in 64% inhibition.

1mM of SEQ ID NO:39 in which the carboxy terminal alanine is alanine amide resulted in 42% inhibition.

1mM of SEQ ID NO:40 in which the carboxy terminal aspartic acid is aspartic acid amide resulted in 72% inhibition.

1mM of SEQ ID NO:41 in which the carboxy terminal glutamic acid is glutamic acid amide resulted in 68% inhibition.

1mM of SEQ ID NO:42 in which the carboxy terminal asparagine is asparagine amide resulted in 40% inhibition.

1mM of SEQ ID NO:43 in which the carboxy terminal leucine is leucine amide resulted in 37% inhibition.

1mM of SEQ ID NO:44 in which the carboxy terminal isoleucine is isoleucine amide resulted in 28% inhibition.

1mM of SEQ ID NO:45 in which the carboxy terminal proline is proline amide resulted in 73% inhibition.

1mM of SEQ ID NO:46 in which the carboxy terminal isoleucine is isoleucine amide resulted in 66% inhibition.

1mM of SEQ ID NO:47 in which the carboxy terminal valine is valine amide resulted in 29% inhibition.

1mM of SEQ ID NO:48 in which the carboxy terminal isoleucine is isoleucine amide resulted in 27% inhibition.

1mM of SEQ ID NO:49 in which the carboxy terminal asparagine is asparagine amide resulted in 26% inhibition.

1mM of SEQ ID NO:50 in which the carboxy terminal serine is serine amide resulted in 29% inhibition.

1mM of SEQ ID NO:51 in which the carboxy terminal proline is proline amide resulted in 68% inhibition.

1mM of SEQ ID NO:52 in which the carboxy terminal serine is serine amide resulted in 63% inhibition.

1mM of SEQ ID NO:53 in which the carboxy terminal proline is proline amide resulted in 63% inhibition.

1mM of SEQ ID NO:54 in which the carboxy terminal valine is valine amide resulted in 52% inhibition.

1mM of SEQ ID NO:55 in which the carboxy terminal histidine is histidine amide resulted in 60% inhibition.

1mM of SEQ ID NO:56 in which the carboxy terminal proline is proline amide resulted in 67% inhibition.

1mM of SEQ ID NO:57 in which the carboxy terminal threonine is threonine amide resulted in 72% inhibition.

1mM of SEQ ID NO:58 in which the carboxy terminal serine is serine amide resulted in 72% inhibition.

1mM of SEQ ID NO:59 in which the carboxy terminal phenylalanine is phenylalanine amide resulted in 73% inhibition.

1mM of SEQ ID NO:60 in which the carboxy terminal proline is proline amide resulted in 73% inhibition.

1mM of SEQ ID NO:61 in which the carboxy terminal proline is proline amide resulted in 72% inhibition.

1mM of SEQ ID NO:62 in which the carboxy terminal proline is proline amide resulted in 62% inhibition.

Example 27

The IC_{50} of SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide was 1.88mM.

The IC_{50} of SEQ ID NO:64 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal arginine is arginine amide was 0.41mM.

The IC_{50} of SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide was 0.29mM.

The IC_{50} of SEQ ID NO:66 in which the carboxy terminal isoleucine is isoleucine amide was 1.02mM.

The IC_{50} of SEQ ID NO:67 in which the amino terminal threonine is acetyl threonine and the carboxy terminal tyrosine is tyrosine amide was 1.13mM.

The IC_{50} of SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide was 2.53mM.

The IC_{50} of SEQ ID NO:69 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal phenylalanine is phenylalanine amide was 1.08mM.

The IC_{50} of SEQ ID NO:70 in which the amino terminal isoleucine is acetyl isoleucine and the carboxy terminal tryptophan is tryptophan amide was 1.11mM.

The IC_{50} of SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide was 0.06mM.

The IC_{50} of SEQ ID NO:72 in which the carboxy terminal phenylalanine is phenylalanine amide was 0.37mM.

The IC_{50} of SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide was 0.85mM.

The IC_{50} of SEQ ID NO:74 in which the carboxy terminal alanine is alanine amide was 0.60mM.

The IC_{50} of SEQ ID NO:75 in which the carboxy terminal glutamine is glutamine amide was 0.31mM.

The IC_{50} of SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide was 0.48mM.

Example 28

The inhibition of binding of TNFα to p55TNFr-IgG chimeric construct was performed as described above using various concentrations of several embodiments of the invention.

The data shown in Figure 1 demonstrates the dose dependent inhibition of TNFα of some embodiments of the invention. The peptides used were:

"C-terminal blocked SEQ ID NO:45" (SEQ ID NO:45 in which the carboxy terminal proline is proline amide);

"C-terminal blocked SEQ ID NO:24" (SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide); and,

"N- and C-terminal blocked SEQ ID NO:11" (SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide).

The data shown in Figure 2 demonstrates the dose dependent inhibition of TNFα of some embodiments of the invention. The peptides used were:

"N- and C-terminal blocked SEQ ID NO:71" (SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide);

"N- and C-terminal blocked SEQ ID NO:65" (SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide);

"N- and C-terminal blocked SEQ ID NO:68" (SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide); and

"N- and C-terminal blocked SEQ ID NO:63" (SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide).

The data shown in Figure 3 demonstrates the dose dependent inhibition of TNFα of some embodiments of the invention. The peptides used were:

"C-terminal blocked SEQ ID NO:73" (SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide);

"C-terminal blocked SEQ ID NO:76 (SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide);

Example 29 TNFα cytotoxicity assays

The ability of the compounds of the invention to bind to the TNF receptor and inhibit activity by human TNFα is tested in a TNFα-mediated cell killing assay. WEHI-164 murine fibrosarcoma cells (Espevik et al., *J. Immunol. Methods* **1986**, *95*, 99-105), or another cell line sensitive to the cytotoxic effects of TNF, are used in the following cytotoxicity assay to identify peptides with TNFα antagonist activity. The cells are grown in Dulbecco's modified Eagle's medium supplemented with 5% heat-inactivated fetal bovine serum, glutamine, nonessential amino acids and sodium pyruvate (DMEM/FBS). The WEHI cells are harvested using a cell scraper and suspend in DMEM/FBS at 1 X 10^6 cells/mL. The cells are then seeded at 50 μL (~5 X 10^4 cells) per well in a 96-well microtiter place. The plate is then incubated for 3-4 hr at 37°C in 5% CO_2 or until 50% confluent.

The peptides to be tested are solubilized at approximately 2.5 mM in 10 mM HEPES pH 7.5 by vortexing and brief sonication. Each peptide is then 0.2 μ filtered and the peptide concentration estimated by measuring the absorbance at 214 nanometers. Two serial threefold dilutions of each peptide

are prepared in 10mM HEPES pH 7.5. Four serial twofold dilutions of an anti-TNFα FAB known to inhibit TNFα activity such as for example cA2 Fab are also prepared in 10mM HEPES pH 7.5 to serve as a positive inhibition control. One-fourth volume of DMEM/FBS containing 10 μg/mL actinomycin D and 500 pg/mL of recombinant human TNFα is then mixed with each dilution of peptide and cA2 Fab, as well as with 10 mM HEPES pH 7.5 (TNF control), and preincubated for 30 minutes at room temperature. A cell control is also prepared in which one-fourth volume of DMEM/FBS containing 10 μg/mL of actinomycin D (but no TNF) is added to 10mM HEPES pH 7.5.

After preincubation, the peptides and controls are transferred (50μL/well) in triplicate to the microtiter wells seeded with WEHI cells and incubated overnight at 37°C in 5% CO_2. Viable cells are detected using a 5 mg/mL solution of 3(4,5-dimethylthiazol-2-yl) 2,5-diphenyl tetrazolium bromide (MTT) in 0.01 M sodium phosphate, 0.15 M sodium chloride pH 7.2. After 0.2μ filtration, 25 μL of the MTT solution is added to each well and incubation continued for 2 hours at 37°C in 5% CO_2. After incubation, the cells and the blue formazan precipitate are solubilized by adding 100 μL/well of 20% (w/v) sodium dodecyl sulfate dissolved in 50% (v/v) dimethylformamide in water. The absorbance at 570 nm (corrected for scatter at 630 nm) is a direct measure of the number of cells that survived in each well. Replicates are averaged and the fraction of cells that survive is calculated based on the absorbance obtained in the cell control wells. The percent inhibition of TNFα activity is then calculated as:

fraction of surviving cells in presence of peptide X [1.0-fraction of surviving cells in TNF control].

Example 30 Treatment of Arthritis, Sepsis, Allograft Rejection and Graft Versus Host Disease

In rheumatoid arthritis, the main presenting symptoms are pain, stiffness, swelling, and loss of function (Bennett JC. The etiology of rheumatoid arthritis, in *Textbook of*

Rheumatology, Kelley WN, Harris ED, Ruddy S, Sledge CB, Eds., WB Saunders, Philadelphia, 1985, pp 879-886). The multitude of drugs used in controlling such symptoms seems largely to reflect the fact that none is ideal. Although there have been many years of intense research into the biochemical, genetic, microbiological, and immunological aspects of rheumatoid arthritis, its pathogenesis is not completely understood, and none of the treatments clearly stop progression of joint destruction (Harris ED, Rheumatoid Arthritis: The clinical spectrum, in *Textbook of Rheumatology*, Kelley WN, Harris ED, Ruddy S, Sledge CB, Eds., WB Saunders, Philadelphia, 1985, pp 915-990).

TNFα is of major importance in the pathogenesis of rheumatoid arthritis. TNFα is present in rheumatoid arthritis joint tissues and synovial fluid at the protein and mRNA level (Buchan G, Barrett K, Turner M, Chantry D, Naini RN, and Feldmann N., Interleukin-1 and tumor necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1α, *Clin. Exp. Immunol.* **1988**, 73, 449-455), indicating local synthesis. However, detecting TNFα in rheumatoid arthritis joints even in quantities sufficient for bioactivation does not necessarily indicate that it is important in the pathogenesis of rheumatoid arthritis, nor that it is a good candidate therapeutic target. In order to address these questions, the effects of anti-TNFα antibody (rabbit or monoclonal) on rheumatoid joint cell cultures, and for comparison, osteoarthritic cell cultures, have been studied. The initial result, that IL-I production was abolished, suggested that TNFα was a therapeutic target for the therapy of rheumatoid arthritis, since anti-TNFα would block both TNFα and IL-I, the two cytokines known to be involved in cartilage and bone destruction (Brennan FM, Chantry D, Jackson A, Maini RN, and Feldmann M, Inhibitory effect of TNFα antibodies on synovial cell interleukin-1 production in rheumatoid arthritis, *Lancet* **1989**, II, 244-247).

Subsequent studies in rheumatoid arthritis tissues have supported this hypothesis. Thus it was found that anti-TNFα

abrogated the production of another proinflammatory cytokine, GM-CSF (Haworth C, Brennan FM, Chantry D, Maini RN, and Feldmann M, GM-CSF expression in rheumatoid arthritis: regulation by tumor necrosis factor alpha, *Eur. J. Immunol.* **1991**, 21, 2575-2579). This observation has been independently confirmed (Alvaro-Gracia et al., *Cytokines in chronic inflammatory arthritis, VI.* **1991**, Analysis of synovial cell involved in granulocyte-macrophage colony-stimulating factor production and gene expression in rheumatoid arthritis and its regulation by IL-I and tumor necrosis factor-α). It has also been demonstrated that anti-TNFα diminishes cell adhesion and HLA class II expression in rheumatoid arthritis joint cell cultures.

Example 31 Treatment of HIV Infection

TNFα is capable of inducing HIV expression in HIV-infected cell lines. See Poli et al., *Proc. Natl. Acad. Sci. USA* **1990** *87*, 782-785 and Butera et al., *J. Immunology* **1993** *150*, 625-634. Butera et al. demonstrated a reduction of induced TNFα production and HIV expression in an infected cell line after treatment with soluble TNF receptors. Thus, the molecules of the present invention may be used to decrease the expression of TNFα and thereby lessen the induction of HIV expression.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
(i) APPLICANT: Heavner, George A.
Kruszynski, Marian
Mervic, Miljenko
Weber, Robert W.
(ii) TITLE OF INVENTION: Tumor Necrosis Factor Inhibitors
(iii) NUMBER OF SEQUENCES: 76
(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & Norris
(B) STREET: One Liberty Place 46th Floor
(C) CITY: Philadelphia
(D) STATE: Pennsylvania
(E) COUNTRY: USA
(F) ZIP: 19403
(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WordPerfect 5.1
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(B) FILING DATE: 01-APR-1994
(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: DeLuca, Mark
(B) REGISTRATION NUMBER: 33,229
(C) REFERENCE/DOCKET NUMBER: CCOR-0232
(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (215) 568-3100
(B) TELEFAX: (215) 568-3439

(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Leu Tyr Asn Asp Ala Pro Gly Pro Gly Gln Asp Thr Asp Ala Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Asp Ala Pro Gly Pro Gly Gln Asp Thr Asp Ala Arg Glu Ala Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Gly Pro Gly Gln Asp Thr Asp Ala Arg Glu Ala Glu Ser Gly Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Gln Asp Thr Asp Ala Arg Glu Ala Glu Ser Gly Ser Phe Thr Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Asp Ala Arg Glu Ala Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Glu Ala Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Lys Glu Met Gly Gln Val Glu Ile Ser Ser Ala Thr Val Asp Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gly Gln Val Glu Ile Ser Ser Ala Thr Val Asp Arg Asp Thr Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Asp Thr Val Ala Gly Ala Arg Lys Asn Gln Tyr Arg His Tyr Trp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Ala Phe Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Leu Phe Gln Ala Phe Asn Ala Ser Leu Ala Leu Asn Gly Thr Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Ala Phe Asn Ala Ser Leu Ala Leu Asn Gly Thr Val His Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ala Phe Asn Ala Ser Leu Ala Leu Asn Gly Thr Val His Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Gln Glu Lys Gln Asn Thr Val Ala Thr Ala His Ala Gly Phe Phe Leu
1 5 10 15

Arg Glu Asn Glu
20

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Lys Gln Asn Thr Val Ala Thr Ala His Ala Gly Phe Phe Leu Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Thr Val Ala Thr Ala His Ala Gly Phe Phe Leu Arg Glu Asn Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Thr Ala His Ala Gly Phe Phe Leu Arg Glu Asn Glu Ala Val Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Ala Gly Phe Phe Leu Arg Glu Asn Glu Ala Val Ser Ala Ser Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:20:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Arg Glu Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu
1 5 10 15

Cys Thr Lys Leu
20

(2) INFORMATION FOR SEQ ID NO:21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Ser Leu Glu Ala Thr Lys Leu Ala Leu Pro Gln Ile Glu Asn Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Leu Ala Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:24:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Ser Glu Asn Leu Phe Gln Ala Phe Asn Ala Ser Leu Ala Leu Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Ala Arg Leu Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Tyr Ala Pro Glu Pro Gly Ser Thr Ala Arg Leu Arg Glu Tyr Tyr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:27:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Glu Pro Gly Ser Thr Ala Arg Leu Arg Glu Tyr Tyr Asp Gln Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ser Thr Ala Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Ala Ala Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:30:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Glu Tyr Tyr Asp Gln Thr Ala Gln Met Ala Ala Ser Lys Ala Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

His Ala Lys Val Phe Ala Thr Lys Thr Ser Asp Thr Val Ala Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:32:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Val Phe Ala Thr Lys Thr Ser Asp Thr Val Ala Asp Ser Ala Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Thr Lys Thr Ser Asp Thr Val Ala Asp Ser Ala Glu Asp Ser Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Ser Asp Thr Val Ala Asp Ser Ala Glu Asp Ser Thr Tyr Thr Gln
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Val Ala Asp Ser Ala Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Ser Ala Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Ala Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Ala Leu Ser Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:39:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Leu Trp Asn Trp Val Pro Glu Ala Leu Ser Ala Gly Ser Arg Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Trp Val Pro Glu Ala Leu Ser Ala Gly Ser Arg Ala Ser Ser Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Glu Ala Leu Ser Ala Gly Ser Arg Ala Ser Ser Asp Gln Val Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Ser Asp Gln Val Glu Thr Gln Ala Ala Thr Arg Glu Gln Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Pro Gly Trp Tyr Ala Ala Leu Ser Lys Gln Glu Gly Ala Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Ala Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Ala Arg Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Ser Asn Thr Thr Ser Ser Thr Asp Ile Ala Arg Pro His Gln Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Thr Ser Ser Thr Asp Ile Ala Arg Pro His Gln Ile Ala Asn Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Thr Asp Ile Ala Arg Pro His Gln Ile Ala Asn Val Val Ala Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ala Arg Pro His Gln Ile Ala Asn Val Val Ala Ile Pro Gly Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Val Ala Ile Pro Gly Asn Ala Ser Arg Asp Ala Val Ala Thr Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:51:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Pro Gly Asn Ala Ser Arg Asp Ala Val Ala Thr Ser Thr Ser Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:52:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Ala Ser Arg Asp Ala Val Ala Thr Ser Thr Ser Pro Thr Arg Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Asp Ala Val Ala Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ala Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:55:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:57:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Ser Thr Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:58:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:59:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:60:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:61:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:62:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:63:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:
Leu Ile Lys Tyr Ala Ser Glu Ser Met Ser Gly Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO:64:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Phe Ser Asn His Trp Met Asn Trp Val Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
1 5 10 15

Lys Ser Ala Val Tyr Leu
20

(2) INFORMATION FOR SEQ ID NO:66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val Ala Glu Ile Arg Ser
1 5 10 15

Lys Ser Ile

(2) INFORMATION FOR SEQ ID NO:67:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Thr Asp Leu Arg Thr Glu Asp Thr Gly Val Tyr Tyr Cys Ser Arg Asn
1 5 10 15

Tyr Tyr Gly Ser Thr Tyr
20

(2) INFORMATION FOR SEQ ID NO:68:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser
20

(2) INFORMATION FOR SEQ ID NO:69:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Tyr Tyr Ser Gln Gln Ser His Ser Trp Pro Phe Thr Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:70:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Ile Asn Thr Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln
1 5 10 15

Ser His Ser Trp
20

(2) INFORMATION FOR SEQ ID NO:71:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Phe Ser Asn His Trp Met Asn Trp
1 5

(2) INFORMATION FOR SEQ ID NO:72:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Tyr Leu Ala His Glu Val Gln Leu Phe Ser Ser Gln Tyr Pro Phe
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:73:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Met Val Tyr Pro Gly Leu Gln Glu Pro Trp Leu His Ser Met Tyr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:74:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Pro Gly Leu Gln Glu Pro Trp Leu His Ser Met Tyr His Gly Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:75:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Gln Glu Pro Trp Leu His Ser Met Tyr His Gly Ala Ala Phe Gln
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:76:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Trp Leu His Ser Met Tyr His Gly Ala Ala Phe Gln Leu Thr Gln
1 5 10 15

CLAIMS

We claim:

1. A peptide comprising an amino acid sequence which consists of 4 to 25 amino acids and which inhibits tumor necrosis factor-alpha activity, wherein said peptide comprises at least a four amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

2. The peptide of claim 1 wherein said peptide consists of 8-20 amino acids.

3. The peptide of claim 1 wherein said peptide consists of 10-15 amino acids.

4. The peptide of claim 1 wherein said peptide is a linear peptide.

5. The peptide of claim 1 wherein said peptide is a conformationally restricted peptide.

6. The peptide of claim 1 wherein said peptide comprises at least a seven amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID

NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76

7. The peptide of claim 1 wherein said peptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

8. The peptide of claim 1 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

9. The peptide of claim 1 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

10. A peptide having an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID

NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

11. The peptide of claim 10 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

12. The peptide of claim 10 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

13. The peptide of claim 12 wherein said peptide is selected from the group consisting of: SEQ ID NO:1 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:2 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:3 in which the carboxy terminal serine is serine amide; SEQ ID NO:4 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:5 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:6 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:7 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:8 in which the carboxy terminal valine is valine amide; SEQ ID NO:9 in which the carboxy terminal tryptophan is tryptophan amide; SEQ ID NO:10 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide; SEQ ID NO:12 in which the amino terminal leucine is acetyl leucine and the carboxy terminal valine is valine amide; SEQ ID NO:13 in which the amino terminal alanine is acetyl alanine and the carboxy terminal serine is serine amide; SEQ ID NO:14 in which the carboxy terminal serine is serine amide; SEQ ID NO:15 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:16 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:17 in

which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:18 in which the carboxy terminal serine is serine amide; SEQ ID NO:19 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:20; SEQ ID NO:21 in which the carboxy terminal valine is valine amide; SEQ ID NO:22 in which the carboxy terminal serine is serine amide; SEQ ID NO:23 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:25 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:26 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:27 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:28 in which the carboxy terminal methionine is methionine amide; SEQ ID NO:29 in which the carboxy terminal serine is serine amide; SEQ ID NO:30 in which the carboxy terminal serine is serine amide; SEQ ID NO:31 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:32 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:33 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:34 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:35 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:36 in which the carboxy terminal proline is proline amide; SEQ ID NO:37 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:38 in which the carboxy terminal glycine is glycine amide; SEQ ID NO:39 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:40 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:41 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:42 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:43 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:44 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:45 in which the carboxy terminal proline is proline amide; SEQ ID NO:46 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:47 in which the carboxy terminal valine is valine amide; SEQ ID NO:48 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:49 in which

the carboxy terminal asparagine is asparagine amide; SEQ ID NO:50 in which the carboxy terminal serine is serine amide; SEQ ID NO:51 in which the carboxy terminal proline is proline amide; SEQ ID NO:52 in which the carboxy terminal serine is serine amide; SEQ ID NO:53 in which the carboxy terminal proline is proline amide; SEQ ID NO:54 in which the carboxy terminal valine is valine amide; SEQ ID NO:55 in which the carboxy terminal histidine is histidine amide; SEQ ID NO:56 in which the carboxy terminal proline is proline amide; SEQ ID NO:57 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:58 in which the carboxy terminal serine is serine amide; SEQ ID NO:59 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:60 in which the carboxy terminal proline is proline amide; SEQ ID NO:61 in which the carboxy terminal proline is proline amide; SEQ ID NO:62 in which the carboxy terminal proline is proline amide, SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:64 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal arginine is arginine amide; SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide; SEQ ID NO:66 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:67 in which the amino terminal threonine is acetyl threonine and the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide; SEQ ID NO:69 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:70 in which the amino terminal isoleucine is acetyl isoleucine and the carboxy terminal tryptophan is tryptophan amide; and SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide, SEQ ID NO:72 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:74 in which the

carboxy terminal alanine is alanine amide; SEQ ID NO:75 in which the carboxy terminal glutamine is glutamine amide; and SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide.

14. A method of inhibiting tumor necrosis factor activity comprising contacting tumor necrosis factor alpha with a peptide that comprises an amino acid sequence which consists of 4 to 25 amino acids and which inhibits tumor necrosis factor-alpha activity, wherein said peptide comprises at least a four amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

15. The method of claim 14 wherein said peptide consists of 8-20 amino acids.

16. The method of claim 14 wherein said peptide consists of 10-15 amino acids.

17. The method of claim 14 wherein said peptide is a linear peptide.

18. The method of claim 14 wherein said peptide is a conformationally restricted peptide.

19. The method of claim 14 wherein said peptide comprises at least a seven amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID

NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76

20. The method of claim 14 wherein said peptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

21. The method of claim 14 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

22. The method of claim 14 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

23. A method of inhibiting tumor necrosis factor activity comprising contacting tumor necrosis factor alpha with a peptide that has an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID

NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

24. The method of claim 23 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

25. The method of claim 23 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

26. The method of claim 23 wherein said peptide is selected from the group consisting of: SEQ ID NO:1 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:2 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:3 in which the carboxy terminal serine is serine amide; SEQ ID NO:4 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:5 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:6 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:7 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:8 in which the carboxy terminal valine is valine amide; SEQ ID NO:9 in which the carboxy terminal tryptophan is tryptophan amide; SEQ ID NO:10 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide; SEQ ID NO:12 in which the amino terminal leucine is acetyl leucine and the carboxy terminal valine is

valine amide; SEQ ID NO:13 in which the amino terminal alanine is acetyl alanine and the carboxy terminal serine is serine amide; SEQ ID NO:14 in which the carboxy terminal serine is serine amide; SEQ ID NO:15 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:16 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:17 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:18 in which the carboxy terminal serine is serine amide; SEQ ID NO:19 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:20; SEQ ID NO:21 in which the carboxy terminal valine is valine amide; SEQ ID NO:22 in which the carboxy terminal serine is serine amide; SEQ ID NO:23 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:25 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:26 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:27 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:28 in which the carboxy terminal methionine is methionine amide; SEQ ID NO:29 in which the carboxy terminal serine is serine amide; SEQ ID NO:30 in which the carboxy terminal serine is serine amide; SEQ ID NO:31 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:32 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:33 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:34 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:35 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:36 in which the carboxy terminal proline is proline amide; SEQ ID NO:37 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:38 in which the carboxy terminal glycine is glycine amide; SEQ ID NO:39 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:40 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:41 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:42 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:43 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:44 in

which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:45 in which the carboxy terminal proline is proline amide; SEQ ID NO:46 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:47 in which the carboxy terminal valine is valine amide; SEQ ID NO:48 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:49 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:50 in which the carboxy terminal serine is serine amide; SEQ ID NO:51 in which the carboxy terminal proline is proline amide; SEQ ID NO:52 in which the carboxy terminal serine is serine amide; SEQ ID NO:53 in which the carboxy terminal proline is proline amide; SEQ ID NO:54 in which the carboxy terminal valine is valine amide; SEQ ID NO:55 in which the carboxy terminal histidine is histidine amide; SEQ ID NO:56 in which the carboxy terminal proline is proline amide; SEQ ID NO:57 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:58 in which the carboxy terminal serine is serine amide; SEQ ID NO:59 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:60 in which the carboxy terminal proline is proline amide; SEQ ID NO:61 in which the carboxy terminal proline is proline amide; SEQ ID NO:62 in which the carboxy terminal proline is proline amide, SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:64 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal arginine is arginine amide; SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide; SEQ ID NO:66 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:67 in which the amino terminal threonine is acetyl threonine and the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide; SEQ ID NO:69 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:70 in which the amino terminal isoleucine is acetyl isoleucine and

the carboxy terminal tryptophan is tryptophan amide; and SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide, SEQ ID NO:72 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:74 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:75 in which the carboxy terminal glutamine is glutamine amide; and SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide.

27. A method of treating an animal suspected of suffering from a disease or disorder mediated by tumor necrosis factor-alpha activity comprising the step of administering to said individual a therapeutically effective amount of a peptide that comprises an amino acid sequence which consists of 4 to 25 amino acids and which inhibits tumor necrosis factor-alpha activity, wherein said peptide comprises at least a four amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

28. The method of claim 27 wherein said peptide consists of 8-20 amino acids.

29. The method of claim 27 wherein said peptide consists of 10-15 amino acids.

30. The method of claim 27 wherein said peptide is a linear peptide.

31. The method of claim 27 wherein said peptide is a conformationally restricted peptide.

32. The method of claim 27 wherein said peptide comprises at least a seven amino acid residue fragment of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76

33. The method of claim 27 wherein said peptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

34. The method of claim 27 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

35. The method of claim 27 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

36. The method of claim 27 wherein said disease or disorder is selected from the group consisting of: sepsis syndrome,

including cachexia; circulatory collapse and shock resulting from acute or chronic bacterial infection; acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections; acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus and rheumatoid arthritis; alcohol-induced hepatitis; chronic inflammatory pathologies such as sarcoidosis and Crohn's pathology; vascular inflammatory pathologies such as disseminated intravascular coagulation; graft-versus-host pathology; Rawasaki's pathology; and malignant pathologies involving tumor necrosis factor-alpha-secreting tumors.

37. A method of treating an animal suspected of suffering from a disease or disorder mediated by tumor necrosis factor-alpha activity comprising the step of administering to said individual a therapeutically effective amount of a peptide that has an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

38. The method of claim 37 wherein said peptide comprises a blocked amino terminal residue and/or a blocked carboxy terminal residue.

39. The method of claim 37 wherein said peptide comprises an acetylated amino terminal residue and/or an amidated carboxy terminal residue.

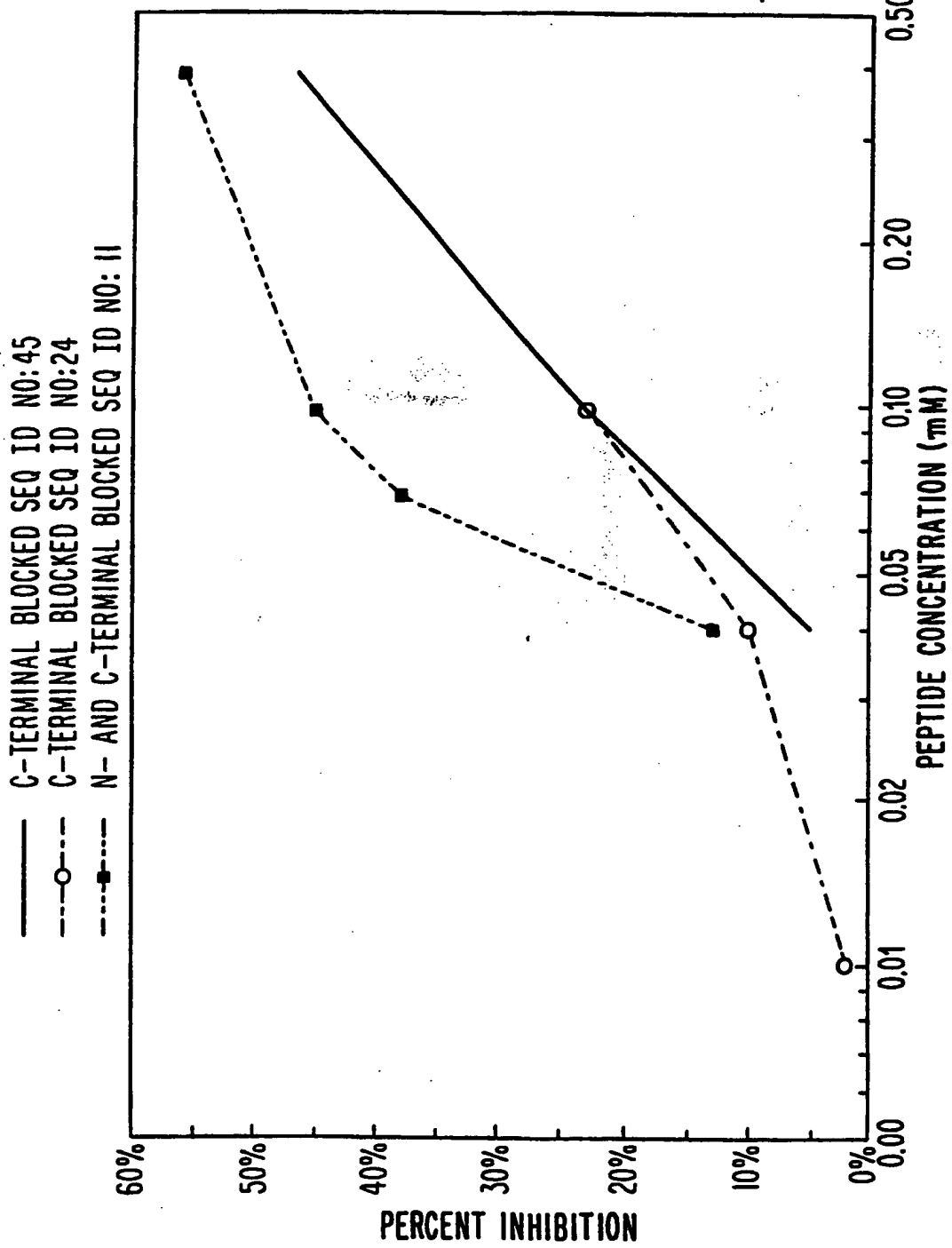
40. The method of claim 37 wherein said peptide is selected from the group consisting of: SEQ ID NO:1 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:2 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:3 in which the carboxy terminal serine is serine amide; SEQ ID NO:4 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:5 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:6 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:7 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:8 in which the carboxy terminal valine is valine amide; SEQ ID NO:9 in which the carboxy terminal tryptophan is tryptophan amide; SEQ ID NO:10 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:11 in which the amino terminal glutamine is acetyl glutamine and the carboxy terminal asparagine is asparagine amide; SEQ ID NO:12 in which the amino terminal leucine is acetyl leucine and the carboxy terminal valine is valine amide; SEQ ID NO:13 in which the amino terminal alanine is acetyl alanine and the carboxy terminal serine is serine amide; SEQ ID NO:14 in which the carboxy terminal serine is serine amide; SEQ ID NO:15 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:16 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:17 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:18 in which the carboxy terminal serine is serine amide; SEQ ID NO:19 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:20; SEQ ID NO:21 in which the carboxy terminal valine is valine amide; SEQ ID NO:22 in which the carboxy terminal serine is serine amide; SEQ ID

NO:23 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:24 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:25 in which the carboxy terminal arginine is arginine amide; SEQ ID NO:26 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:27 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:28 in which the carboxy terminal methionine is methionine amide; SEQ ID NO:29 in which the carboxy terminal serine is serine amide; SEQ ID NO:30 in which the carboxy terminal serine is serine amide; SEQ ID NO:31 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:32 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:33 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:34 in which the carboxy terminal glutamine is glutamine amide; SEQ ID NO:35 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:36 in which the carboxy terminal proline is proline amide; SEQ ID NO:37 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:38 in which the carboxy terminal glycine is glycine amide; SEQ ID NO:39 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:40 in which the carboxy terminal aspartic acid is aspartic acid amide; SEQ ID NO:41 in which the carboxy terminal glutamic acid is glutamic acid amide; SEQ ID NO:42 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:43 in which the carboxy terminal leucine is leucine amide; SEQ ID NO:44 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:45 in which the carboxy terminal proline is proline amide; SEQ ID NO:46 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:47 in which the carboxy terminal valine is valine amide; SEQ ID NO:48 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:49 in which the carboxy terminal asparagine is asparagine amide; SEQ ID NO:50 in which the carboxy terminal serine is serine amide; SEQ ID NO:51 in which the carboxy terminal proline is proline amide; SEQ ID NO:52 in which the carboxy terminal serine is serine amide; SEQ ID NO:53 in which the carboxy terminal proline is proline amide; SEQ ID NO:54 in which the carboxy

terminal valine is valine amide; SEQ ID NO:55 in which the carboxy terminal histidine is histidine amide; SEQ ID NO:56 in which the carboxy terminal proline is proline amide; SEQ ID NO:57 in which the carboxy terminal threonine is threonine amide; SEQ ID NO:58 in which the carboxy terminal serine is serine amide; SEQ ID NO:59 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:60 in which the carboxy terminal proline is proline amide; SEQ ID NO:61 in which the carboxy terminal proline is proline amide; SEQ ID NO:62 in which the carboxy terminal proline is proline amide, SEQ ID NO:63 in which the amino terminal leucine is acetyl leucine and the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:64 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal arginine is arginine amide; SEQ ID NO:65 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal arginine is arginine amide; SEQ ID NO:66 in which the carboxy terminal isoleucine is isoleucine amide; SEQ ID NO:67 in which the amino terminal threonine is acetyl threonine and the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:68 in which the amino terminal aspartic acid is acetyl aspartic acid and the carboxy terminal serine is serine amide; SEQ ID NO:69 in which the amino terminal tyrosine is acetyl tyrosine and the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:70 in which the amino terminal isoleucine is acetyl isoleucine and the carboxy terminal tryptophan is tryptophan amide; and SEQ ID NO:71 in which the amino terminal phenylalanine is acetyl phenylalanine and the carboxy terminal tryptophan is tryptophan amide, SEQ ID NO:72 in which the carboxy terminal phenylalanine is phenylalanine amide; SEQ ID NO:73 in which the carboxy terminal tyrosine is tyrosine amide; SEQ ID NO:74 in which the carboxy terminal alanine is alanine amide; SEQ ID NO:75 in which the carboxy terminal glutamine is glutamine amide; and SEQ ID NO:76 in which the carboxy terminal glutamine is glutamine amide.

41. The method of claim 37 wherein said disease or disorder is selected from the group consisting of: sepsis syndrome, including cachexia; circulatory collapse and shock resulting from acute or chronic bacterial infection; acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections; acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus and rheumatoid arthritis; alcohol-induced hepatitis; chronic inflammatory pathologies such as sarcoidosis and Crohn's pathology; vascular inflammatory pathologies such as disseminated intravascular coagulation; graft-versus-host pathology; Rawasaki's pathology; and malignant pathologies involving tumor necrosis factor-alpha-secreting tumors.

Fig. 1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C-TERMINAL BLOCKED SEQ ID NO:24
N- AND C-TERMINAL BLOCKED SEQ ID NO: 11
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20%
10%
0%
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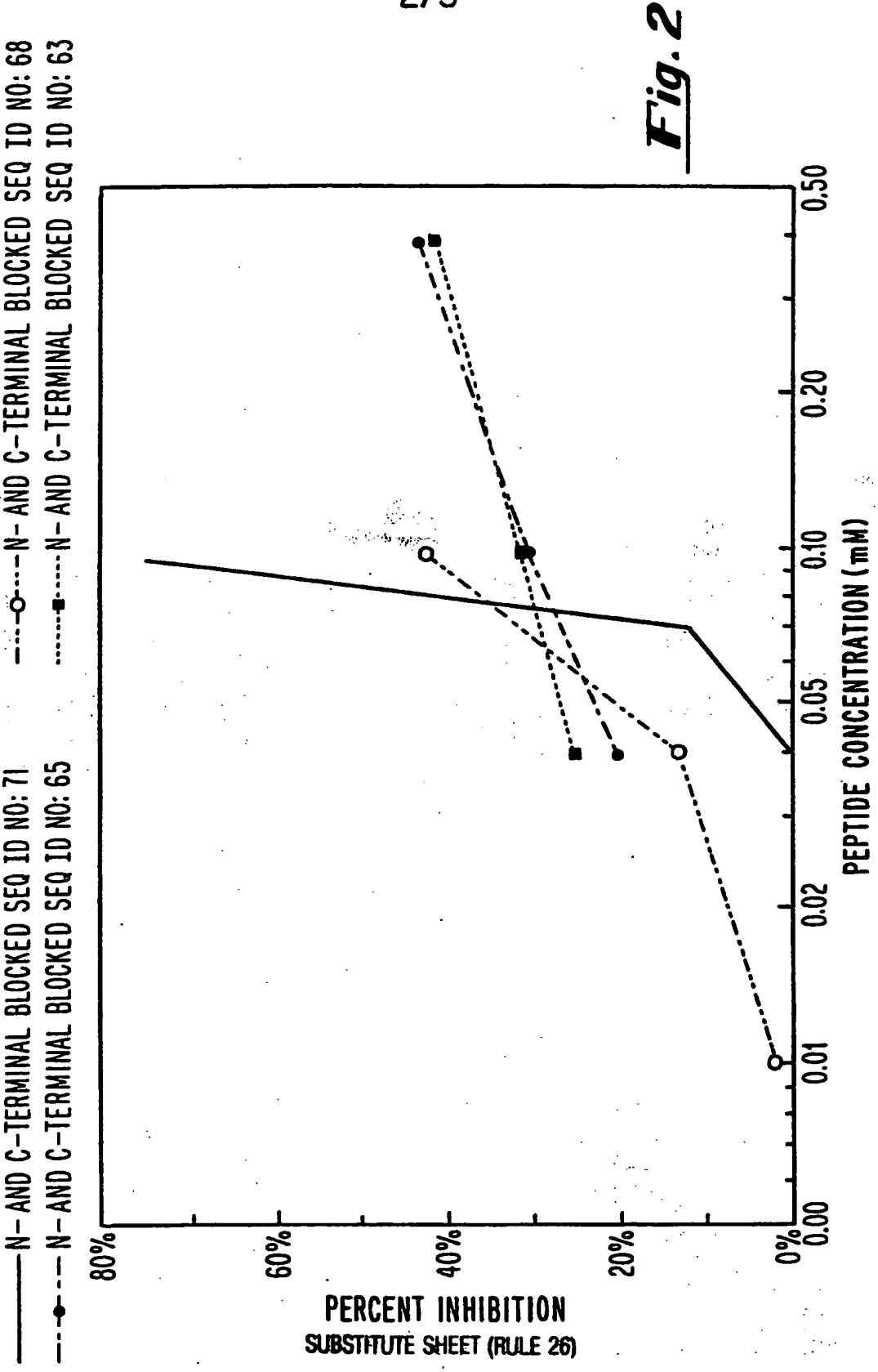
PEPTIDE CONCENTRATION (mM)

Fig. 2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N- AND C-TERMINAL BLOCKED SEQ ID NO: 63
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40%
20%
0%
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0.02
0.05
0.10
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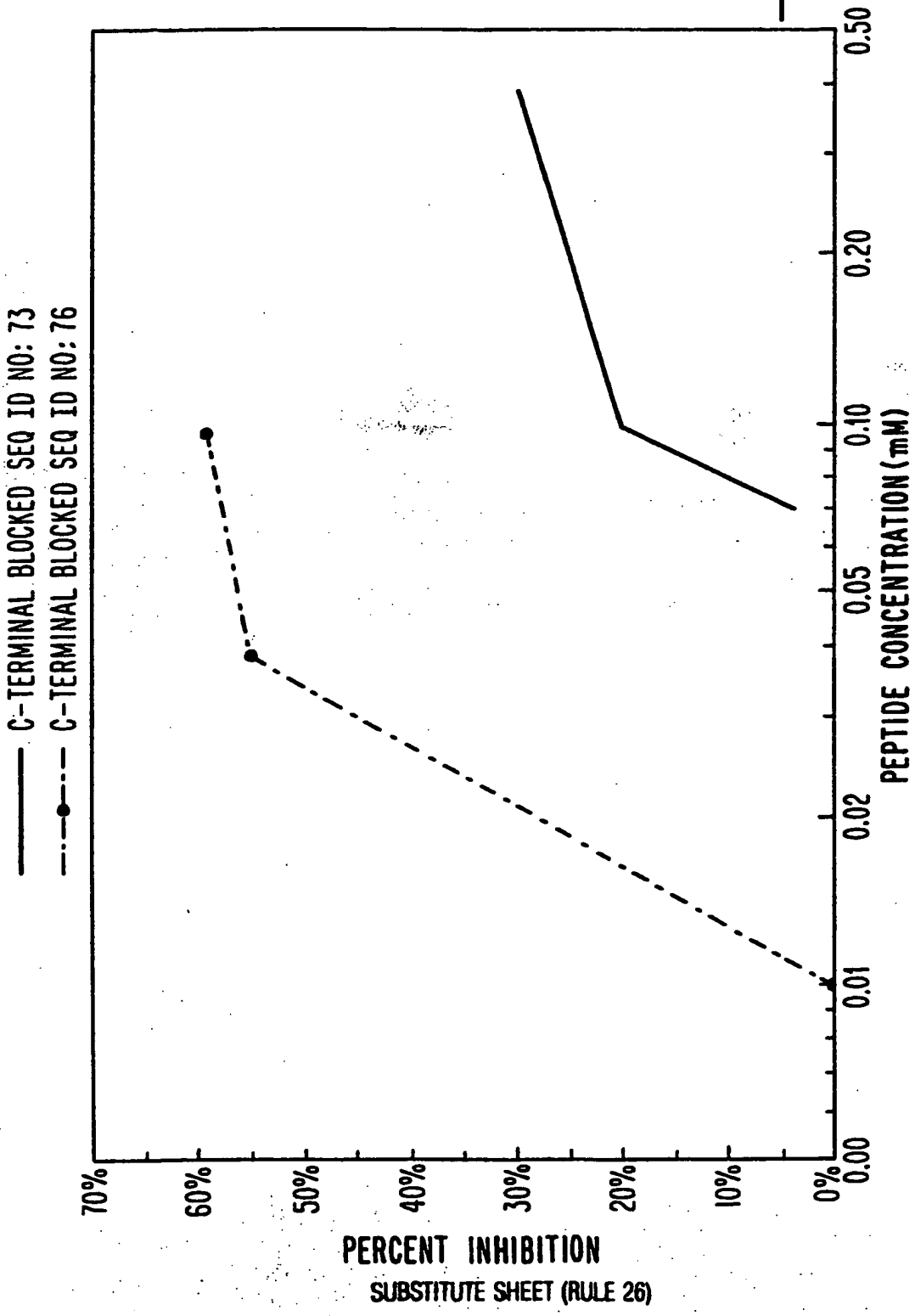
PEPTIDE CONCENTRATION (mM)

Fig. 3


C-TERMINAL BLOCKED SEQ ID NO: 73
C-TERMINAL BLOCKED SEQ ID NO: 76
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50%
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30%
20%
10%
0%
PEPTIDE CONCENTRATION (mM)
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0.02
0.05
0.10
0.20
0.50

INTERNATIONAL SEARCH REPORT

Im. ational application No.
PCT/US95/04018

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :IPC(6) :A61K 38/00; C07K 7/04
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : U.S. CL :530/324, 326, 327, 328, 329, 330; 514/12, 13, 14, 15, 16, 17, 18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CHEMICAL ABSTRACTS, APS, GENBANK

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Immunology, Volume 141, Number 5, issued 01 September 1988, Eilat et al., "V region sequences of anti-DNA and anti-RNA autoantibodies from NZB/NZW F1 mice", pages 1745-1753, see entire article.	1-41
A	Cancer Research, Volume 49, issued 01 April 1989, Foon, K.A., "Biological response modifiers: the new immunotherapy", pages 1621-1638, see entire document.	1-41

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 JULY 1995	26 JUL 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENET PRICKRIL Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US95/04018

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

U.S. CL :530/324, 326, 327, 328, 329, 330; 514/12, 13, 14, 15, 16, 17, 18

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